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(54) Title: BIARYL COMPOUNDS, THEIR PREPARATION AND THEIR USE IN THERAPY

(57) Abstract: The invention relates to biaryl compounds, their preparation and their use in the treatment of bacterial and viral infection.

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(57) Abstract: The invention relates to biaryl compounds, their preparation and their use in the treatment of bacterial and viral infection.

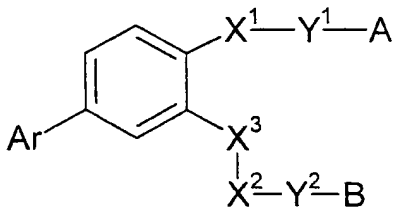
BIARYL COMPOUNDS, THEIR PREPARATION AND THEIR USE IN THERAPY

The present invention relates to a class of chemical compounds, their preparation and their use in therapy, particularly in the treatment of viral and bacterial infection.

Although many pharmaceutical compounds and compositions are available for the treatment of viral and bacterial infections, there remains a continuing need for improved treatments.

The present inventors have discovered a new class of chemical compounds which are particularly useful in the treatment of viral and bacterial infection.

According to the present invention there is provided a compound of the formula



wherein

Ar is an aryl group,

X^1 is selected from O, S, SO, SO_2 and NR,

X^2 is selected from O, S, SO, SO_2, NR and CR_2,

X^3 is CR_2,

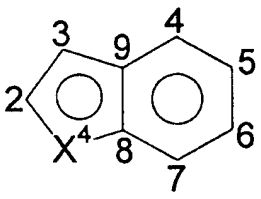
Y^1 and Y^2 are independently selected from C_{1-12} alkylene, C_{4-12} arylene, C_{4-16} aralkylene, $CO(C_{1-12}$ alkylene), $CO(C_{4-12}$ arylene) and $CO(C_{4-16}$ aralkylene) groups,

A and B are independently selected from groups comprising a group selected from:

amine ($-NR_2$), amide ($-CONR_2$), amidine ($-C(=NR)NR_2$), thioamide ($-CSNR_2$), oxime (=NOR), hydroxylamine (-NHOR), hydroxamic acid (-CONROR), hydrazine ($-NRNR_2$), hydrazone ($=NNR_2$), sulphonamide ($-SO_2NR_2$), sulphinamide ($-SONR_2$), sulphoximine ($-SO(=NR)-$), urea ($-NRCONR_2$), guanidine ($-NRC(=NR)NR_2$), and aromatic and non-aromatic nitrogen heterocyclic groups.

each R is independently selected from H, C_{1-12} alkyl and C_{3-12} aryl, or any two R groups may together comprise a C_{1-6} alkylene chain,
and pharmaceutically acceptable derivatives thereof.

In the compounds of the present invention Ar is an aryl group as herein defined. Preferably, the aryl group is a monocyclic or fused polycyclic (preferably bicyclic such as [6,5], [6,6] and [5,5] systems) aromatic or heteroaromatic group. Aromatic groups include phenyl and naphthyl. Heteroaromatic groups are generally preferred to the corresponding aromatic group. Heteroaromatic groups may comprise one or more heteroatoms. Monocyclic heteroaromatic groups include pyridyl, pyrrolyl, furanyl, thienyl and thiazolyl. Heteroaromatic groups may be bonded to the rest of the molecule either via a ring carbon atom or via a ring heteroatom. Preferred fused bicyclic heteroaromatic groups include [6,5] (such as indolyl, indolinyl, benzofuranyl, benzothienyl), [6,6] (such as quinolinyl, isoquinolinyl, quinoxalinyl) and [5,5] fused bicyclic heteroaromatic groups. [6,5] ring systems, in which a heteroatom may be located at any ring position, are preferred. Particularly preferred fused bicyclic heteroaromatic groups comprise groups of the structure:



wherein X^4 is NH, S or O. Indoles (i.e. where X^4 is NH) are preferred.

Bicyclic heteroaromatic groups of this structure may be bonded to the rest of the molecule via any position, bonding via the 2, 3, 5 or 6 position being preferred.

The group Ar may be substituted as herein defined. Where substituted, there are preferably one to three substituents, more prefereably one substituent.

X^1 may be O, S, SO, SO_2 or NR. Preferably, X^1 is O.

X^2 may be O, S, SO, SO_2, NR or CR_2. Preferably, X^2 is NR, more preferably NH.

X^3 is CR_2. Preferably, X^3 is CH_2.

Y^1 and Y^2 are independently selected from C_{1-12} alkylene, C_{4-12} arylene, C_{4-16} aralkylene, $CO(C_{1-12}$ alkylene), $CO(C_{4-12}$ arylene) and $CO(C_{4-16}$ aralkylene) groups, as herein defined.

Preferably, Y^1 comprises a direct chain of 1 to 5 carbon atoms linking X^1 and A. For example, if Y^1 is an ethylene or *o*-phenylene group, the direct chain linking X^1 and A has two carbon atoms. Preferably, Y^1 comprises a C_{1-5} alkylene group.

Preferably, Y^2 comprises a direct chain of 1 to 5 carbon atoms linking X^2 and B. Preferably, Y^2 comprises a C_{1-5} alkylene group.

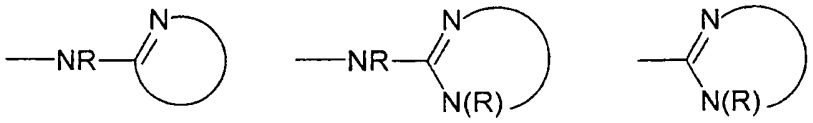
A and B are independently selected from groups comprising a group selected from amine ($-NR_2$), amide ($-CONR_2$), amidine ($-C(=NR)NR_2$), thioamide ($-CSNR_2$), oxime (=NOR), hydroxylamine (-NHOR), hydroxamic acid (-CONROR), hydrazine ($-NRNR_2$), hydrazone ($=NNR_2$), sulphonamide ($-SO_2NR_2$), sulphinamide ($-SONR_2$), sulphoximine (-SO(=NR)-), urea ($-NRCONR_2$), guanidine ($-NRC(=NR)NR_2$), and aromatic and non-aromatic nitrogen heterocyclic groups.

Preferably, A and B are independently selected from groups comprising a group selected from amine, amidine, guanidine, and aromatic and non-aromatic nitrogen heterocyclic groups. Preferably, the amine, amidine and guanidine groups are unsubstituted (i.e. R=H).

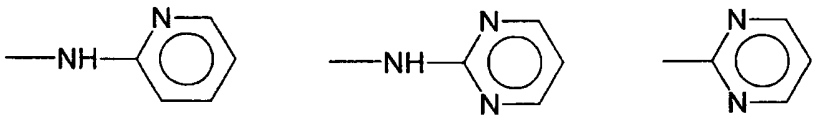
The aromatic and non-aromatic nitrogen heterocyclic groups may be monocyclic (preferably 5 or 6 membered rings) or polycyclic (preferably fused bicyclic, more preferably [6,5], [6,6] and [5,5] systems) and may comprise one or more nitrogen atom. Examples of aromatic nitrogen heterocyclic groups include pyrrolyl, pyridinyl, 2-,3- and 4-pyrimidinyl, quinolinyl, isoquinolinyl, indolinyl, benzodiazolyl, benzotriazolyl, imidazolyl, triazolyl and thiazolyl groups. Examples of non-aromatic nitrogen heterocyclic groups include pyrrolidinyl, pyrrolidinone, piperidinyl, morpholinyl and piperazinyl groups. The aromatic and non-aromatic nitrogen heterocyclic groups may be substituted or unsubstituted. Preferred substituents include amino groups ($-NR_2$). The aromatic and non-

aromatic nitrogen heterocyclic group may be bonded to the rest of the molecule via a ring carbon atom or via a ring nitrogen atom or via a substituent.

Included within the scope of the term aromatic and non-aromatic nitrogen heterocyclic groups are cyclic groups which mimic amidine or guanidine groups of the general formulae



Specific examples include 2-aminopyridine, 2-aminopyrimidine and 2-pyrimidine groups:



Each R is independently selected from H, C_{1-12} alkyl and C_{3-12} aryl, or any two R groups may together comprise a C_{1-6} alkylene chain. For example, an R group in X^2 may be combined with an R group in B such that together with Y^2 a cyclic link is formed between X^2 and B.

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where acyclic, the alkyl group is preferably a C_{1-12} , more preferably C_{1-4} chain. Where cyclic, the alkyl group is preferably a C_{3-12}, more preferably C_{5-10} and more preferably comprises a C_5, C_6 or C_7 ring. The alkyl chain or ring may include (i.e. be optionally interrupted with and/or terminate with) one or more heteroatoms, such as oxygen, sulphur or nitrogen.

As used herein the term "alkylene" means a branched or unbranched, cyclic or acylic, saturated or unsaturated divalent hydrocarbyl radical. Where acyclic the alkylene group is preferably a C_{1-12}, more preferably C_{1-5} chain. Where cyclic, the alkylene group is

preferably a C_{3-12}, more preferably C_{5-10}, more preferably comprises a C_5, C_6 or C_7 ring. The alkylene chain or ring may include (i.e. be interrupted and/or terminate with) one or more heteroatoms such as oxygen, sulfur or nitrogen.

As used herein, the term "aryl" means a C_{3-26}, preferably C_{3-12}, aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl, thienyl, thiazolyl, indolyl, indolinyl, benzofuranyl, benzothienyl, quinolinyl, isoquinolinyl, quinoxalinyl, 2-, 3- or 4-pyrimidinyl, benzodiazolyl, benzotriazolyl, imidazolyl, triazolyl and thiazolyl groups.

As used herein the term "arylene" means a divalent hydrocarbyl radical comprising a C_{3-12} aromatic group (such as *o-*, *m- or p*-phenylene) or heteroaromatic group containing one or more, preferably one, heteroatom (such as a pyridine-2,3-diyl group).

As used herein the term "aralkylene" means a divalent hydrocarbyl radical comprising both alkylene and arylene groups (such as $-CH_2$-(*o*-phenylene)-CH_2-).

The alkyl, aryl, alkylene, arylene and aralkylene groups Ar, Y^1, Y^2 and R, and the groups A and B, may be further substituted or unsubstituted. For example, a C_1 (methyl) group may be further substituted with a phenyl group to give a benzyl group. Substituents may include carbon containing groups such as alkyl, aryl, aralkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl); halogen atoms (e.g. F, Cl, Br and I) and halogen containing groups such as haloalkyl (e.g.trifluoromethyl); oxygen containing groups such as alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl), ethers (e.g. alkoxy, alkoxyalkyl, aryloxyalkyl), aldehydes (e.g. carboxaldehyde), ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl), acids (e.g. carboxy, carboxyalkyl), acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonylyoxy, alkylcarbonylyoxyalkyl) and amides (e.g. aminocarbonyl, mono- or dialkylaminocarbonyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, arylaminocarbonyl); and carbamates (eg. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or dialkylaminocarbonyloxy, arylaminocarbonyloxy), and ureas (eg. mono- or dialkylaminocarbonylamino or arylaminocarbonylamino); nitrogen containing groups such

as amines (e.g. amino, mono- or dialkylamino, aminoalkyl, mono- or dialkylaminoalkyl), azides, nitriles (e.g. cyano, cyanoalkyl), nitro; sulfur containing groups such as thiols, thioethers, sulfoxides, and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and heterocyclic groups containing one or more, preferably one, heteroatom (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As used herein, the term "alkoxy" means alkyl-O- and "alkanoyl" means alkyl-CO. Alkyl substituent groups or alkyl-containing substituent groups may comprise one or more further substituents. As used herein, the term "aryloxy" means aryl –O- and "aryloyl" means aryl –CO. Aryl substituent groups or aryl-containing substituent groups may comprise one or more further substituents.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, addition compound, or any other compound which upon administration to a recipient is capable of providing (directly or indirectly) a compound of the present invention or a pharmaceutically acceptable metabolite. By "pharmaceutically acceptable metabolite" is meant a metabolite or residue of a compound of the present invention which gives rise to a biological activity exhibited by the present compounds.

As used herein, a "patient" is a mammal (e.g., such as a human being or other non-human mammal) to whom a compound according to the invention is administered. The term

"patient" does not imply that the individual has ever been hospitalized for medical treatment.

As used herein, a "microorganism" refers to a bacterial, viral, prokaryotic or eukaryotic organism which can be viewed microscopically. The term "microorganism" as used herein encompasses both bacteria and viruses.

As used herein, "anti-microbial properties" or "anti-bacterial properties" or "anti-viral properties" refer to the ability of the compounds according to the invention to inhibit microbial, bacterial, viral growth. As defined herein, "inhibiting growth" refers to an inhibition in the translation of microbial proteins, which in turn results in an inhibition in microbial replication (and therefore transcription of microbial mRNAs) which in turn results in an inhibition of infection. Any one of these processes (e.g., translation, replication, transcription, infection) may be assayed to determine the effectiveness of the compounds according to the invention (e.g., defined as the ability of the compound to inhibit growth). As defined herein, "inhibition of microbial growth" refers to an at least two-fold decrease in any of the parameters discussed above (e.g., translation of microbial proteins, replication of microorganisms, transcription of microbial mRNAs, and/or infection by microorganisms). Inhibition can also refer to an at least two fold decrease in an immune response associated with a microbial infection (e.g., such as the accumulation of anti-microbial antibodies or cytokines and/or pyrogens associated with microbial infection). In one embodiment, inhibition is at least 2-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, or at least 100-fold.

In a preferred embodiment of the invention, the compound inhibits translation of a bacterial and/or viral transcript. In still a more preferred embodiment, the compound inhibits translation of a bacterial and/or viral transcript while not inhibiting translation of a mammalian transcript. In one embodiment of the invention, translation is inhibited at least 2-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, or at least 100-fold compared to translation of bacterial and/or viral transcripts in a mammalian organism which has not been treated with the compounds according to the invention. In a further embodiment, the compound inhibits bacterial and/or viral replication.

According to a further aspect of the present invention there is provided a compound according to the present invention for use in a method of treatment, preferably in the prophylaxis or treatment of viral infection or bacterial infection.

According to a further aspect of the present invention there is provided use of a compound according to the present invention in the manufacture of a medicament for the prophylaxis or treatment of viral infection or bacterial infection.

According to a further aspect of the present invention there is provided a method of prophylaxis or treatment of viral infection or bacterial infection comprising administration to a patient in need of such treatment an effective dose of a compound according to the present invention.

In one embodiment, the effective dose of the compound according to the invention is a dose effective to decrease the titer of infectious microorganisms in a patient's body. In one embodiment, the titer of infectious microorganisms is measured by culturing a bodily sample and counting the number of microorganisms in the sample. In another embodiment, the titer of infectious microorganisms is determined by measuring the expression of the bacterial or viral nucleic acids and/or proteins. In a further embodiment, the effective dose of the compound is a dose effective to restore the immune response of a host (e.g., a patient) to a microorganism to normal (e.g., to resemble an immune response of an uninfected host). For example, in one embodiment, a bodily fluid from a patient is assayed to detect the presence and/or amounts of anti-bacterial or antiviral antibodies.

In one embodiment, a compound according to the invention is administered to a patient who has both a bacterial and a viral infection. In one embodiment, the patient treated has AIDS. In another embodiment, the person has AIDS and at least one opportunistic infection.

In another embodiment, a compound according to the invention is used prophylactically. In one embodiment, the compound is contacted with a cell or surface thereby to prevent the growth of microorganisms in proximity to the cell or surface. In one embodiment, the compound is administered to a patient to prevent infection by a microorganism or to reduce

the severity of infection (e.g., as measured by determining the titer of the microorganism in a treated vs. an untreated individual).

Viral infections include, but are not limited to:

Family	*Virus*	*Disease*
Adenoviruses	Adenovirus	acute respiratory disease
Arenaviruses	Lassa Virus	Lassa Fever
Astroviridae	Astrovirus	Enteritis
Bunyaviridae	Hantavirus Phlebovirus	Hantavirus Pulmonary Syndrome Rift Valley Fever
Calciviridae	Hepatitis E	
Filoviridae	Ebola Virus Marburg Virus	
Flaviviridae	Japanese Encephalitis Virus Hepatitis C Virus Dengue Virus Yellow Fever Virus Hepatitis G Virus	 Dengue Haemorrhagic Fever
Hepadnaviridae	Hepatitis B Virus Hepatitis D (delta) Virus	
Herpesviridae	Herpes Simplex Virus 1 Herpes Simplex Virus 2 Cytomegalovirus (CMV) Epstein Barr Virus (EBV) Varicello Zoster Virus (VZV) HHV-6 HHV-7 KSHV/HHV8	 Mononucleosis Chicken Pox/Shingles Kaposi Sarcoma
Orthomyxoviruses	Influenza Virus	
Paramyxoviridae	Paramyxoviruses Rubulaviruses Morbilliviruses Respiratory Syncytial Virus	Para-Influenza Mumps Measles
Papovaviridae	Papillomaviruses Polyomaviruses BK and JC Virus	Warts/Cervical Cancer
Parvoviridae	Parvoviruses	Erythema Infectiosum
Picornaviridae	Coxsackie Viruses (A and B)	Viral Myocarditis & Meningitis & Enteritis

	Hepatitis A Virus	Hepatitis
	Polioviruses	Poliomyelitis
	Rhinoviruses	Cold
Reoviridae	Astroviruses	Diarrhoea
	Caliciviruses	Diarrhoea
	Reoviruses	Diarrhoea
Rhabdoviridae	Lyssavirus	Rabies
Retroviridae	HIV-1 and HIV-2	AIDS
	HTLV-1 and HTLV-2	Leukaemia

Preferably, the viral infection comprises HIV or HCV infection, more preferably HIV-I or HIV-II.

Bacterial infections include, but are not limited to, infections by *Gram Positive Bacteria* including Bacillus cereus, Bacillus anthracis, Clostridium botulinum, Clostridium difficile, Clostridium tetani, Clostridial perfringens, Corynebacteria diphtheriae, Enterococcus (Streptococcus D), Listeria Monocytogenes, Pneumoccoccal Infections (Streptococcus pneumoniae), Staphylococcal Infections and Streptococcal Infections; *Gram Negative Bacteria* including Bactcroides, Bordetella pertussis, Brucella, Campylobacter Infections, Enterohemmorrhagic Escherichia coli (EHEC/E.coli O157:H7), Enteroinvasive Escherichia coli (EIEC), Enterotoxigenic Escherichia coli (ETEC), Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumonia, Legionella spp., Moraxella catarrhalis, Neisseria gonnorrhoeae, Neisseria meningitidis, Proteus spp., Pseudomonas aeruginosa, Salmonella spp., Shigella spp., Vibrio cholera and Yersinia; *Acid Fast Bacteria* including Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Mycobacterium leprae, Atypical Bacteria, Chlamydia, Mycoplasma, Rickettsia, Spirochetes, Treponema pallidum, Borrelia recurrentis, Borrelia burgdorfii and Leptospira icterohemorrhagiae; and other miscellaneous bacteria including Actinomyces and Nocardia.

It is a feature of the compounds of the present invention that they inhibit the binding of the HIV protein Tat to the HIV RNA Tar binding site. Accordingly, the present invention further provides use of a compound of the present invention to inhibit the binding of Tat to Tar.

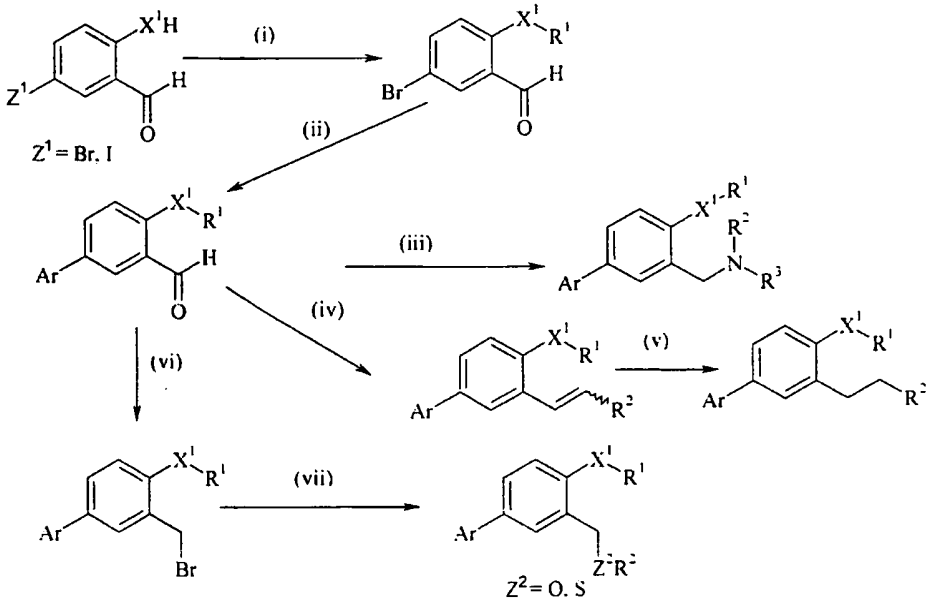
It is also feature of the compounds of the present invention that they inhibit translation of bacterial proteins. Accordingly, the present invention further provides use of a compound of the present invention to inhibit the translation of bacterial proteins.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

According to a further aspect of the present invention there is provided a method of preparing a pharmaceutical composition comprising the step of combining a compound of the present invention with a pharmaceutically acceptable excipient.

According to a further aspect of the present invention there is provided a process for the preparation of the compounds of the present invention. The compounds of the present invention may be prepared according to the following general reaction scheme.

General Reaction Scheme



Reagents (i) R^1halide. Cs_2CO_3; (ii) $ArB(OH)_2$, Pd catalyst; (iii) R^2R^3NH, DCE or EtOH, reducing agent; (iv) $R^2CH_2Br^- Ph_3P^+$, base, toluene; (v) H_2, Pd/C, solvent; (vi) (a) $NaBH_4$, solvent, (b) Ph_3P, CBr_4; (vii) HZ^2R^2, base, solvent.

The biaryl compounds according to the invention have anti-microbial (e.g., anti-bacterial and/or anti-viral properties). In one embodiment, the compounds inhibit microbial growth. Inhibition of microbial growth can be assayed in a number of different ways. In one embodiment, microbial growth is measured by assaying the translation of microbial proteins, levels of microbial replication, transcription of microbial mRNAs, and infectivity (e.g., viral titer in cells exposed to a virus). Assays for measuring such parameters are well known in the art and include, but are not limited to, immunossays to detect translation products or assays which measure binding of translational regulators to mRNA transcripts (e.g., to measure translation), RT-PCT, or hybridization assays (e.g., to measure transcription), incorporation of labeled nucleotides or hybridization assays to measure the presence/amount of microbial genomic DNA (e.g., to measure replication), plate counting assays (e.g., to measure microbial titers), and the like.

In one embodiment, compounds are synthesized according to the methods described above and the ability of the compounds to inhibition of microbial growth is assayed to identify compounds which produce an at least two-fold decrease in any of the parameters discussed above (e.g., translation of microbial proteins, replication of microorganisms, transcription of microbial mRNAs, and/or infection by microorganisms). In one embodiment, inhibition is at least 2-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, or at least 100-fold. In one embodiment, activity is measured *in vitro*, e.g., by measuring the effects of the compounds on bacterial cultures or on cells infected or to be infected with a virus. In another embodiment, compounds are selected which inhibit the growth of both bacterial and viral microorganisms. In one embodiment, compounds are selected which inhibit the growth of HIV in cells infected or to be infected with the virus. In still another embodiment, compounds are selected which inhibit the growth of HIV and any of the characteristic microorganisms found in opportunistically infected AIDS patients.

In another embodiment, compounds according to the invention are tested in animal models to determine the effects of the compounds on microbial growth as described above. In one

embodiment, the compounds are tested for their affect on the immune response of an animal to a microbial infection to select compounds which return the immune response to normal (e.g., provide a response similar to that observed in an animal which has not been infected. For example, in one embodiment, a bodily fluid (e.g., blood) is obtained from an infected animal at various time points after administering a compound according to the invention to determine the presence or absence of antibodies specific for microbial antigens and/or the presence or absence of cytokines characteristic of microbial infection. Additionally, or alternatively, the animal may be tested by evaluating any of the parameters discussed above (e.g., translation of microbial proteins, replication of microorganisms, transcription of microbial mRNAs, and/or infection by microorganisms).

In a preferred embodiment, the compounds according to the invention inhibit translation of a bacterial and/or viral transcript. In still a more preferred embodiment, the compound inhibits translation of a bacterial and/or viral transcript while not inhibiting translation of a mammalian transcript. In one embodiment of the invention, translation is inhibited at least 2-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, or at least 100-fold compared to translation of bacterial and/or viral transcripts in a mammalian organism which has not been treated with the compounds according to the invention. In one embodiment, a reporter gene is cloned downstream an in frame with a bacterial or viral translation initiation sequence, and the activity of the compounds synthesised is assayed by monitoring the presence and/or amount of the protein encoded by the reporter gene.

In a preferred embodiment, a compound according to the invention is provided which inhibits the binding of the HIV protein Tat to the HIV RNA Tar binding site. Accordingly, the present invention further provides use of a compound of the present invention to inhibit the binding of Tat to Tar. In one embodiment, inhibition is measured directly by measuring binding of Tat to Tar. In another embodiment, inhibition is measured by measuring the production of Tat protein.

In another embodiment, the compounds according to the invention are tested for their ability to prevent microbial infection. For example, in one embodiment, the compounds are contacted to a cell and the ability of a microorganism to grow in proximity to said cell

is evaluated. In one embodiment, the cell is a cell which is to be infected with a virus, and the cell is contacted with the compound prior to contacting the cell with the virus. The ability of the compounds to be used prophylactically is then evaluated as described above (e.g., by assaying one or more of translation of microbial proteins, replication of microorganisms, transcription of microbial mRNAs, and/orinfection by microorganisms). In a further embodiment, the compounds according to the invention are contacted with a surface and assayed for their ability to prevent microbial growth on the surface.

The medicament employed in the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredients mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredients is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

The compounds of the invention may also be presented as liposome formulations.

In general a suitable dose will be in the range of 0.01 to 100 mg per kilogram body weight of the recipient per day, preferably in the range of 0.2 to 10 mg per kilogram body weight per day. The desired dose is preferably presented once daily, but may be dosed as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

In a preferred method according to the present invention, the compounds are used to prevent or delay the onset of HIV-infection in individuals who are susceptible or at risk of HIV-infection (e.g., intravenous drug users, patients who have had, or are about to receive, a blood transfusion, immunodeficient or immunocompromised patients, gay men, and the like) The method comprises administering to such a patient a prophylactically effective amount (which generally is the same as a therapeutically effective amount) of one or more of the compositions according to the present invention to the patient to delay or prevent an HIV-infection. In another embodiment of the invention, the compounds are used to treat an already-infected patient (e.g., an HIV-positive patient) to prevent re-infection and to inhibit viral replication and/or further infection by opportunistic microorganisms. The

compounds may be used by themselves or in conjunction with other drugs (e.g., protease inhibitors, antibiotics) or other therapies.

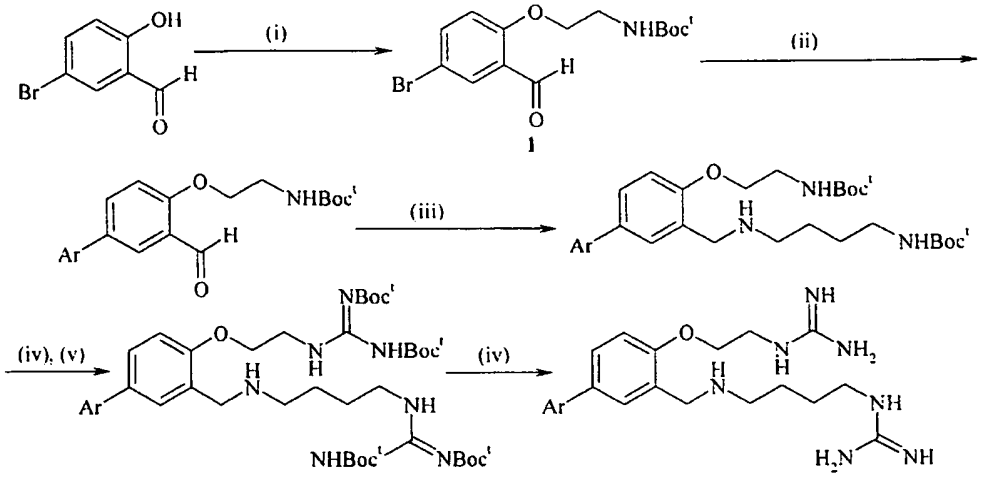
The invention will now be described with reference to the following Examples. It will be appreciated that what follows is by way of example only and that modifications to detail may be made whilst still falling within the scope of the invention.

EXPERIMENTAL

Chemical Synthesis

The compounds of the present invention were synthesized according to the following protocols and characterized by standard spectroscopic techniques including LCMS under the following conditions.

HPLC:	HP1100
Column:	ABZ+, 3.3cm*4.6mmD
Temperature:	20°C
Solvents:	A - Water + 0.1% formic acid + 10mmol ammonium acetate
	B – 95% Acetonitrile/water + 0.05% formic acid
Flow rate:	1mL/min
Gradient:	Total time 8 minutes
	- 100% A for 0.7 minutes
	- ramp up to 100% B over 3.5 minutes
	- 100% B for 3.5 minutes
	- ramp down to 0% B over 0.3 minutes
Detection:	UV detection at 230nm, 254nm and 270nm
Mass spec:	HP1100 MSD
Method:	Electrospray, +ve ion

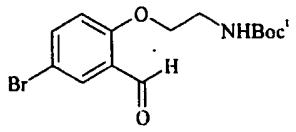


Reagents: (i) $BrCH_2CH_2NHBoc$, Cs_2CO_3, DMF; (ii) $ArB(OH)_2$, $PdCl_2(PPh_3)_2$, DME, Na_2CO_3; (iii) $BocNH(CH_2)_4NH_2$, DCE, sodium triacetoxyborohydride; (iv) TFA/DCM, 1/1; (v) *N,N'*-bis-*t*-butoxycarbonylpyrazolecarboxamidine, *N,N*-diisopropylethylamine, CH_3CN.

Scheme 1

The following examples were synthesized using the procedures outlined in Scheme 1.

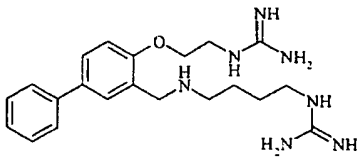
Example 1



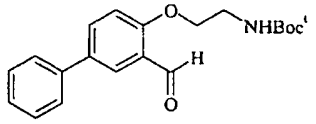
To 5-bromosalicylaldehyde (1eq.) and cesium carbonate (2 eq.) in DMF at RT was added 1-bromo-2-*N*-*t*-butoxycarbonylethane (1.2 eq.), and the mixture stirred overnight at RT. The DMF was evaporated *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave **1** as a solid, which was crystallized from hexane.

LC retention time 4.56 minutes. $[M+H]^+$ 345.

Example 2



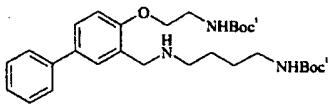
a)



To a mixture of the aldehyde of example 1 (1 eq.), dichlorobis(triphenylphosphine)-palladium(II) (10mol%) and 2N Na_2CO_3 (eq.) was added phenylboronic acid (1.5eq.) in dry, degassed DME and the mixture heated at 80°C for 16h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 4.75 minutes, $[M+Na]^+$ 364.

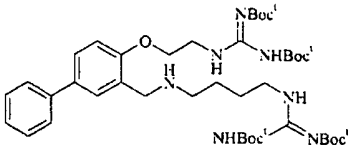
b)



The aldehyde (1 eq.) and mono-*N*-*t*-butoxycarbonyl-1,4-diaminobutane (2 eq.) were stirred at RT for 15min in 1,2-dichloroethane, and then sodium triacetoxyborohydride (1.5 eq.) was added. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 3.79 minutes, $[M+H]^+$ 514.

c)



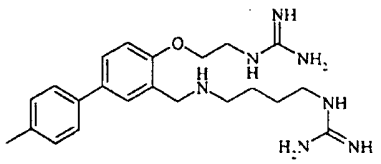
The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* and the TFA salt used without further purification. The TFA salt was stirred in acetonitrile, treated with excess *N,N*-diisopropylethylamine and *N,N'*-bis-*t*-butoxycarbonylpyrazole carboxamidine added. The mixture was stirred overnight at RT then concentrated *in vacuo*. The residue was partitioned between dichloromethane and water, the organic layer washed with brine and dried over $MgSO_4$. Concentration gave an oil, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 4.44 minutes, $[M+H]^+$ 799.

d) The fully protected bis-guanidine was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired bis-guanidine as the tris-trifluoroacetate.

LC retention time 0.53 and 2.64 minutes, $[M+H]^+$ 398.

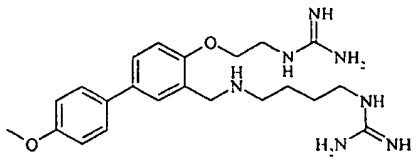
Example 3



As example 2 using *p*-tolylboronic acid.

LC retention time 2.78 minutes, $[M+H]^+$ 412.

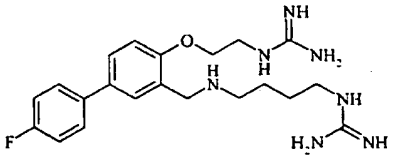
Example 4



As example 2 using 4-methoxyphenylboronic acid.

LC retention time 2.71 minutes, $[M+H]^+$ 428.

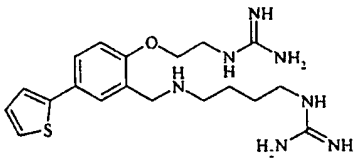
Example 5



As example 2 using 4-fluorophenylboronic acid.

LC retention time 2.71 minutes, $[M+H]^+$ 416.

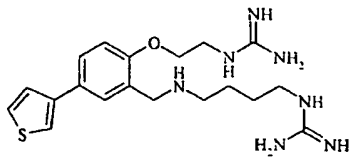
Example 6



As example 2 using 2-thienylboronic acid.

LC retention time 0.50 and 2.62 minutes, $[M+H]^+$ 404.

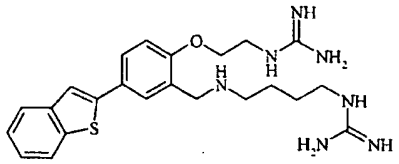
Example 7



As example 2 using 3-thienylboronic acid.

LC retention time 0.51 and 2.58 minutes, $[M+H]^+$ 404.

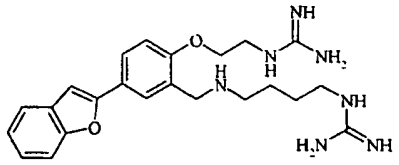
Example 8



As example 2 using benzo[b]thiophene-2-boronic acid.

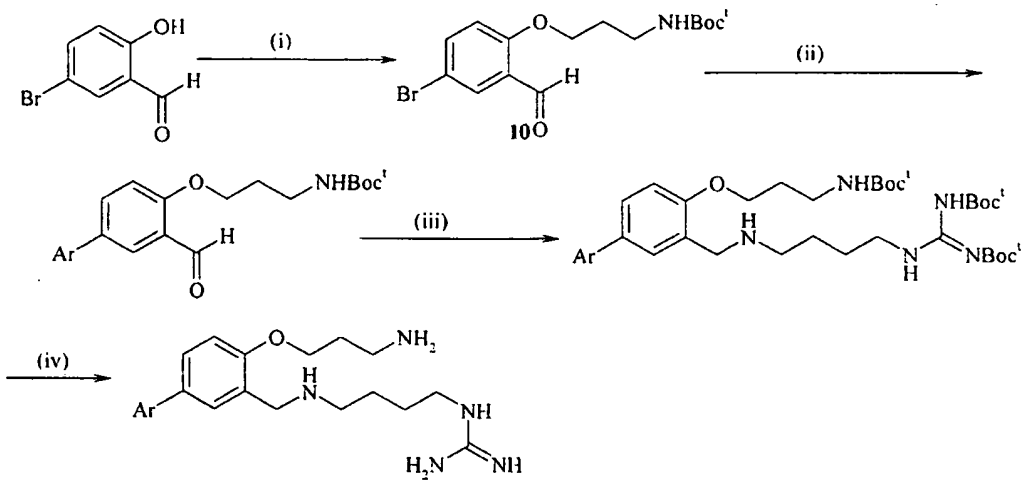
LC retention time 2.92 minutes, $[M+H]^+$ 454.

Example 9



As example 2 using benzo[b]furan-2-boronic acid.

LC retention time 2.85 minutes, $[M+H]^+$ 438.

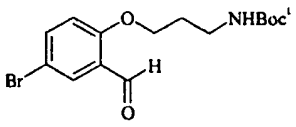


Reagents: (i) $Br(CH_2)_3NHBoc$, Cs_2CO_3, DMF; (ii) $ArB(OH)_2$, $PdCl_2(PPh_3)_2$, DME, Na_2CO_3; (iii) (*N,N'*-bis-*t*- butoxycarbonylcarboxamidine)$NH(CH_2)_4NH_2$, DCE, sodium triacetoxyborohydride; (iv) TFA/DCM, 1/1.

Scheme 2

The following examples were synthesized using the procedures outlined in Scheme 2.

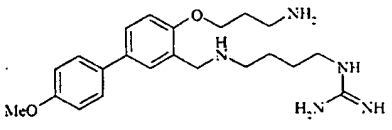
Example 10



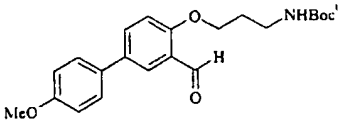
To 5-bromosalicylaldehyde (1 eq) and cesium carbonate (2 eq) in DMF at RT was added 1-bromo-3-*N*-*t*-butoxycarbonylpropane (1.2) and the mixture stirred overnight at RT. The DMF was evaporated *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave the desired aldehyde as a solid. which was crystallized from hexane.

LC retention time 4.68 minutes. $[M+H]^+$ 380.

Example 11



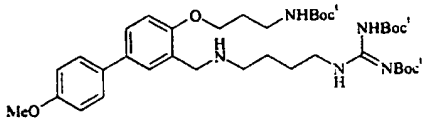
a)



To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added *p*-tolylboronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 16h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 4.79 minutes, $[M+H\text{-}Boc]^+$ 286.

b)



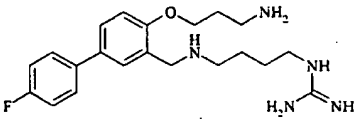
The aldehyde (1 eq) and 1-amino-4-*N*,*N*'-bis-*t*-butoxycarbonylguanidinobutane (1.8 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5 eq) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 4.18 minutes, $[M+H]^+$ 700.

c) The tris-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired mono-guanidine as the tris-trifluoroacetate.

LC retention time 2.69 minutes, $[M+H]^+$ 400.

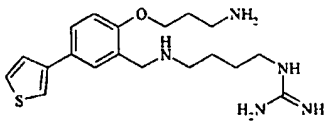
Example 12



As example 11 using 4-fluorophenylboronic acid.

LC retention time 2.68 minutes, $[M+H]^+$ 388.

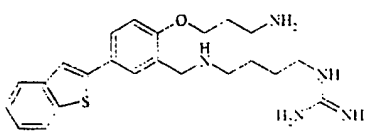
Example 13



As example 11 using 3-thienylboronic acid.

LC retention time 0.49 and 2.56 minutes, $[M+H]^+$ 376.

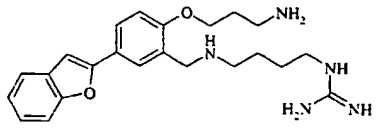
Example 14



As example 11 using benzo[b]thiophene-2-boronic acid.

LC retention time 2.91 minutes, $[M+H]^+$ 426.

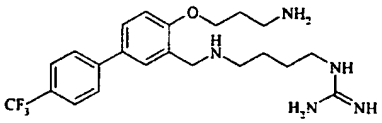
Example 15



As example 11 using benzo[b]furan-2-boronic acid.

LC retention time 2.84 minutes, $[M+H]^+$ 410.

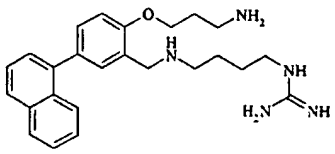
Example 16



As example 11 using 4-trifluoromethylbenzeneboronic acid.

LC retention time 2.90 minutes, $[M+H]^+$ 438.

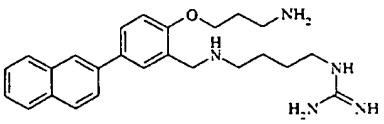
Example 17



As example 11 using naphthyl-1-boronic acid.

LC retention time 2.87 minutes, $[M+H]^+$ 420.

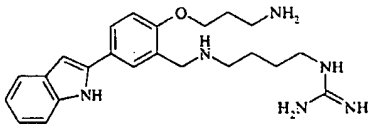
Example 18



As example 11 using naphthyl-2-boronic acid.

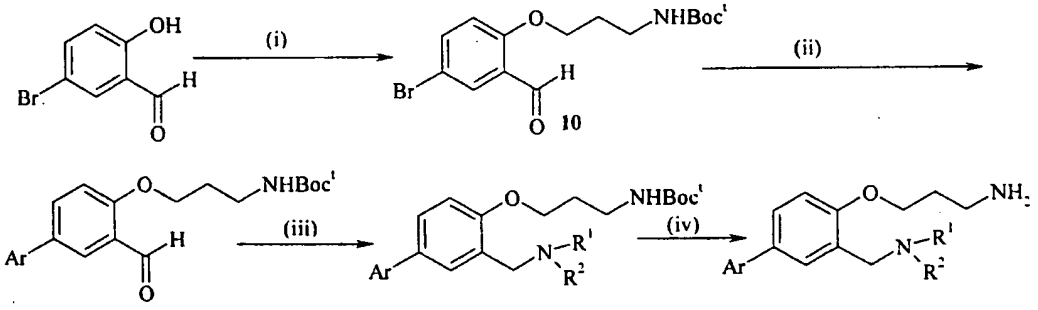
LC retention time 2.87 minutes, $[M+H]^+$ 420.

Example 19



As example 11 using 1-*N*-Boc-indole-2-boronic acid.

LC retention time 2.76 minutes, $[M+H]^+$ 410.

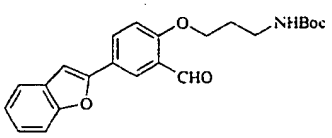


Reagents: (i) $Br(CH_2)_3NHBoc$, Cs_2CO_3, DMF; (ii) $ArB(OH)_2$, $PdCl_2(PPh_3)_2$, DME, Na_2CO_3; (iii) $R^1R^2NH_2$, DCE, sodium triacetoxyborohydride; (iv) TFA/DCM, 1/1.

Scheme 3

The following examples were synthesized using the procedures outlined in Scheme 3.

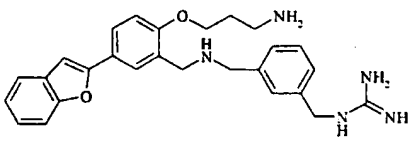
Example 20



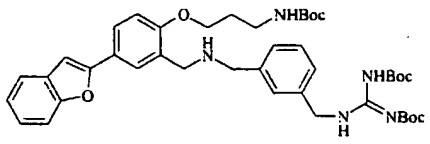
To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added benzo[*b*]furan-2-boronic acid acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 16h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.17 minutes, $[M+Na]^+$ 418.

Example 21



a)



The aldehyde (1 eq.) from example 20 and mono-*N,N'*-bis-*t*-butoxycarbonylguanidino-*m*-xylenediamine (2 eq.) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5 eq.) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$.

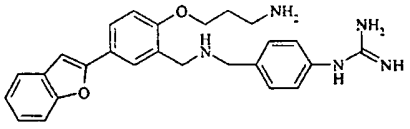
Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 4.38 minutes, $[M+H]^+$ 758.

b) The tris-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired mono-guanidine as the tris-trifluoroacetate.

LC retention time 2.90 minutes, $[M+H]^+$ 458.

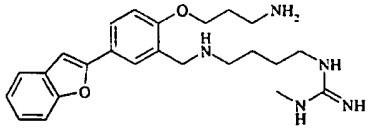
Example 22



As example 21 using 4-*N,N'*-bis-*t*-butoxycarbonylguanidinoaminomethylaniline.

LC retention time 2.82 minutes, $[M+H]^+$ 444.

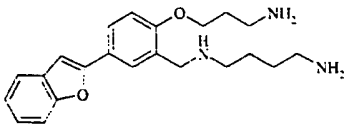
Example 23.



As example 21 using 1-amino-4-[(*N,N'*-bis-t-butoxycarbonyl)-*N*-methyl] guanidinobutane.

LC retention time 2.78 minutes, $[M+H]^+$ 424.

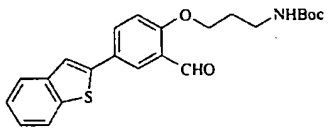
Example 24



As example 21 using mono-*N*-*t*-butoxycarbonyldiaminobutane.

LC retention time 2.74 minutes. $[M+H]^+$ 368.

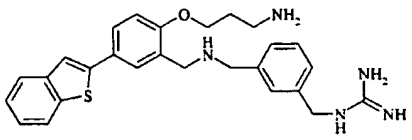
Example 25



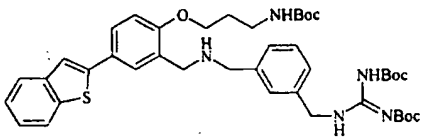
To a mixture of the aldehyde of example 10 (1 eq.), dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added benzo[*b*]thiophene-2-boronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 16h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.30 minutes, $[M+H\text{-}Boc]^+$ 312.

Example 26



a)



The aldehyde (1 eq.) from Example 25 and mono-*N,N'*-bis-*t*-butoxycarbonylguanidino-*m*-xylenediamine (2 eq.) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5 eq.) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$.

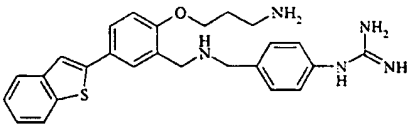
Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 4.50 minutes, $[M+H]^+$ 760.

b) The tris-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired mono-guanidine as the tris-trifluoroacetate.

LC retention time 2.90 minutes, $[M+H]^+$ 460.

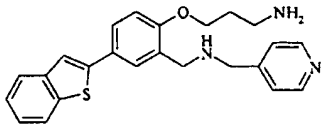
Example 27



As example 26 using 4-*N,N'*-bis-*t*-butoxycarbonylguanidinoaminomethylaniline.

LC retention time 2.90 minutes, $[M+H]^+$ 460.

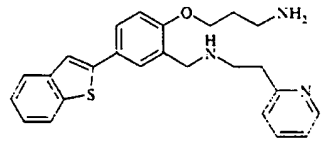
Example 28.



As example 26 using 4-aminomethylpyridine.

LC retention time 3.09 minutes, $[M+H]^+$ 404.

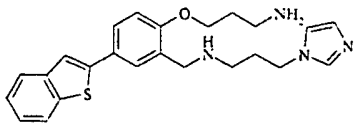
Example 29.



As example 26 using 2-(2-aminoethyl)pyridine.

LC retention time 3.19 minutes, $[M+H]^+$ 418.

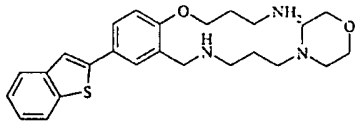
Example 30.



As example 26 using 1-(3-aminopropyl)imidazole.

LC retention time 2.87 minutes, $[M+H]^+$ 421.

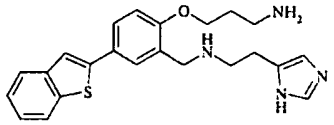
Example 31.



As example 26 using 1-(3-aminopropyl)morpholine.

LC retention time 2.86 minutes, $[M+H]^+$ 440.

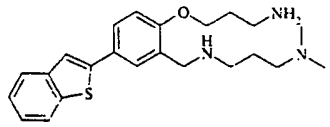
Example 32.



As example 26 using 5-(2-aminoethyl)imidazole.

LC retention time 2.86 minutes, $[M+H]^+$ 407.

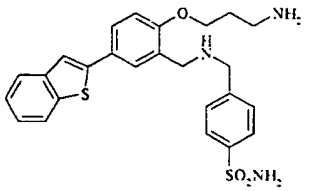
Example 32.



As example 26 using N,N-1,3-diaminopropane.

LC retention time 2.84 minutes, $[M+H]^+$ 398.

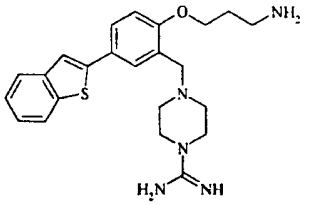
Example 33.



As example 26 using 4-aminomethylbenzenesulfonamide.

LC retention time 3.15 minutes, $[M+H]^+$ 482.

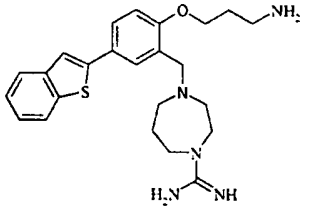
Example 34.



As example 26 using mono-*N,N'*-bis-Boc-piperazine carboxamidine.

LC retention time 2.92 minutes, $[M+H]^+$ 424.

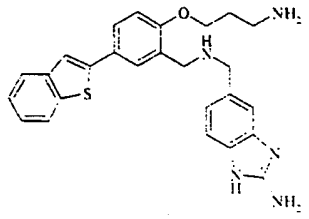
Example 35.



As example 26 using mono-*N,N'*-bis-Boc-homopiperazine carboxamidine.

LC retention time 2.83 minutes, $[M+H]^+$ 438.

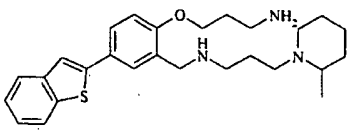
Example 36.



As example 26 using 5-aminomethyl-2-*N*-Boc-aminobenzimidazole.

LC retention time 2.89 minutes, $[M+H]^+$ 458.

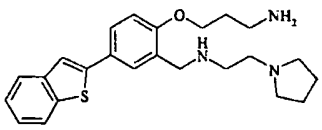
Example 37.



As example 26 using 1-(3-aminopropyl)-2-methylpiperidine.

LC retention time 2.93 minutes, $[M+H]^+$ 452.

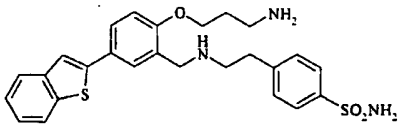
Example 38.



As example 26 using 1-(2-aminoethyl)pyrrolidine.

LC retention time 2.90 minutes, $[M+H]^+$ 410.

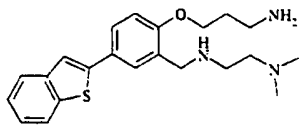
Example 39.



As example 26 using 4-(2-aminoethyl)benzene sulfonamide.

LC retention time 3.18 minutes, $[M+H]^+$ 496.2

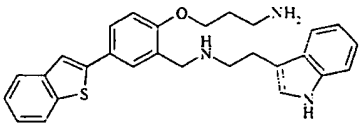
Example 40.



As example 26 using *N,N*-dimethyl-1,2-diaminoethane.

LC retention time 2.89 minutes, $[M+H]^+$ 384.

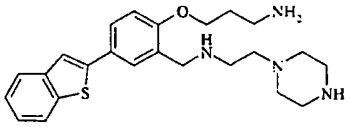
Example 41.



As example 26 using tryptamine.

LC retention time 3.36 minutes, $[M+H]^+$ 456.

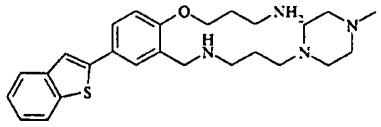
Example 42.



As example 26 using 1-(2-aminoethyl)-4-*N*-Boc-piperazine.

LC retention time 2.83 minutes, $[M+H]^+$ 425.

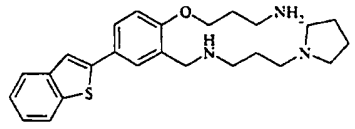
Example 43.



As example 26 using 1-(3-aminopropyl)-4-methylpiperazine.

LC retention time 2.86 minutes, $[M+H]^+$ 453.

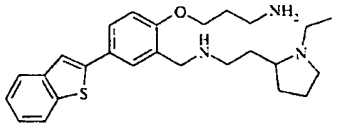
Example 44.



As example 26 using 1-(3-aminopropyl)pyrrolidine.

LC retention time 2.87 minutes, $[M+H]^+$ 424.

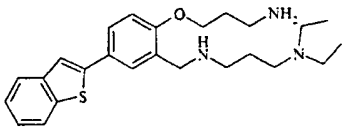
Example 45.



As example 26 using 2-aminoethyl-1-ethylpyrrolidine.

LC retention time 2.95 minutes, $[M+H]^+$ 424.

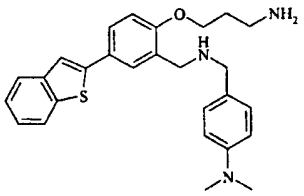
Example 46.



As example 26 using *N,N*-diethyl-1,3-diaminopropane.

LC retention time 2.88 minutes, $[M+H]^+$ 426.

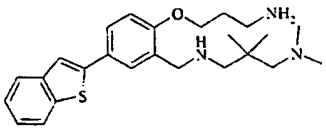
Example 47.



As example 26 using 4-aminomethyl-*N,N*-dimethylaniline.

LC retention time 3.34 minutes, $[M+H]^+$ 446.

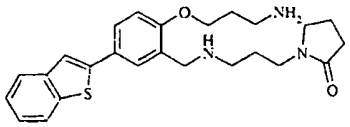
Example 48.



As example 26 using *N,N*-dimethyl-2,2-dimethyl-1,3-diaminopropane.

LC retention time 2.93 minutes. $[M+H]^+$ 426.

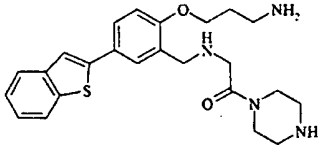
Example 49.



As example 26 using 1-(3-aminopropyl)pyrrolidinone.

LC retention time 3.12 minutes, $[M+H]^+$ 438.

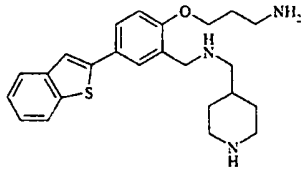
Example 50.



As example 26 using 4-*N*-Boc-piperazine glycinamide.

LC retention time 2.82 minutes, $[M+H]^+$ 439.

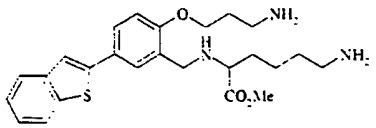
Example 51.



As example 26 using 4-aminomethyl-1-*N*-Boc-piperidine.

LC retention time 2.93 minutes, $[M+H]^+$ 410.

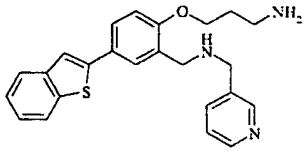
Example 52.



As example 26 using δ-*N*-Boc-D,L-lysine methyl ester.

LC retention time 2.94 minutes, $[M+H]^+$ 456.

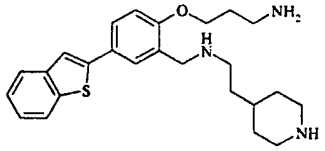
Example 53.



As example 26 using 3-aminomethylpyridine.

LC retention time 2.93 minutes, $[M+H]^+$ 404.

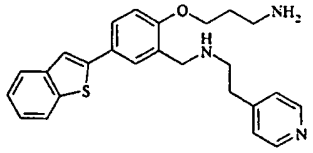
Example 54.



As example 26 using 4-(2-aminoethyl)-*N*-Boc-piperidine.

LC retention time 2.87 minutes, $[M+H]^+$ 424.

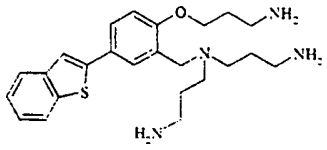
Example 55.



As example 26 using 4-(2-aminoethyl)pyridine.

LC retention time 2.99 minutes, $[M+H]^+$ 418.

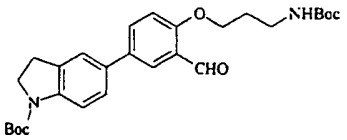
Example 56.



As example 26 using bis-(2-*N*-Boc-aminoethyl)amine.

LC retention time 0.62 minutes, $[M+H]^+$ 427.

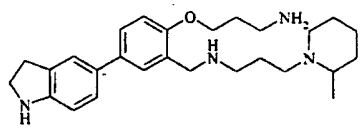
Example 57



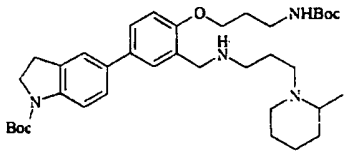
To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added 1-*N*-*t*-butoxycarbonylindoline-5-boronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 1h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.23 minutes, $[M+H\text{-}Boc]^+$ 397.

Example 58



a)



The aldehyde (1 eq) from example 57 and 1-(3-aminopropyl)-2-methylpiperidine (1.6) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5) was added in one portion. After stirring for 16h at RT the mixture was concentrated

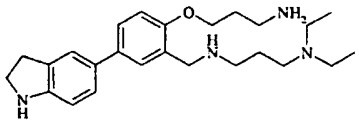
in vacuo and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 3.47 minutes, $[M+H]^+$ 637.

b) The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10 min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 0.58 minutes, $[M+H]^+$ 437.

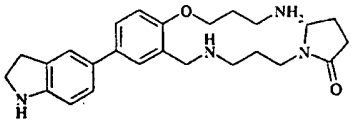
Example 59



As example 58 using *N,N*-diethyldiaminopropane.

LC retention time 0.52 and 0.84 minutes, $[M+H]^+$ 411.

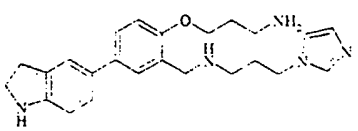
Example 60



As example 58 using 1-(3-aminopropyl)pyrrolidinone.

LC retention time 0.56 and 2.60 minutes, $[M+H]^+$ 423.

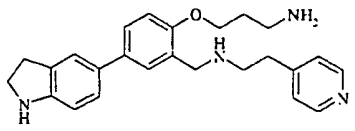
Example 61



As example 58 using 1-(3-aminopropyl)imidazole.

LC retention time 0.54 and 0.78 minutes, $[M+H]^+$ 406.

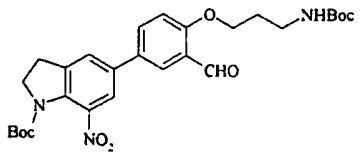
Example 62



As example 58 using 4-(2-aminoethyl)pyridine.

LC retention time 0.57 minutes, $[M+H]^+$ 403.

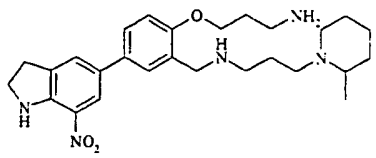
Example 63



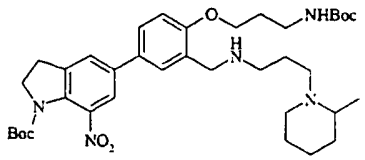
To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added 1-*N*-*t*-butoxycarbonyl-7-nitroindoline-5-boronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 1h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.03 minutes, $[M+H\text{-}Boc]^+$ 442.

Example 64



a)



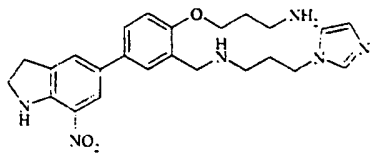
The aldehyde (1 eq) from example 63 and 1-(3-aminopropyl)-2-methylpiperidine (1.6 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5 eq) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 4.10 minutes, $[M+H]^+$ 754.

b) The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 2.84 minutes, $[M+H]^+$ 482.

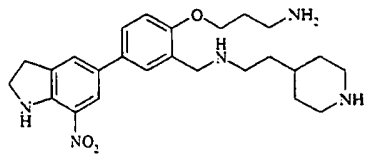
Example 65



As example 64 using 1-(3-aminopropyl)imidazole.

LC retention time 2.82 minutes, $[M+H]^+$ 451.

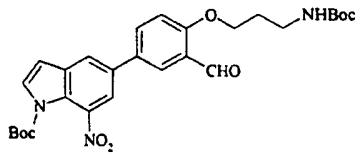
Example 66



As example 64 using 4-(2-aminoethyl)-1-*N*-Boc-piperidine.

LC retention time 2.81 minutes, $[M+H]^+$ 454.

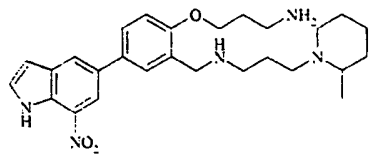
Example 67



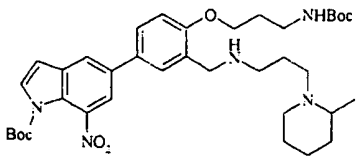
To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added 1-*N*-*t*-butoxycarbonyl-7-nitroindole-5-boronic acid in (2 eq) dry, degassed DME and the mixture heated at 80°C for 1h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.20 minutes, $[M+H\text{-}Boc]^+$ 440.

Example 68



a)



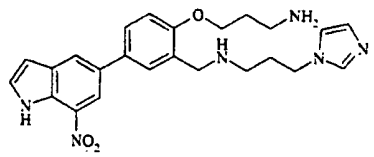
The aldehyde (1 eq) from example 67 and 1-(3-aminopropyl)-2-methylpiperidine (1.6 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5 eq) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 3.50 minutes, $[M+H]^+$ 680.

b) The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10 min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 2.88 minutes, $[M+H]^+$ 480.

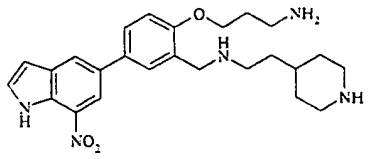
Example 69



As example 68 using 1-(3-aminopropyl)imidazole.

LC retention time 2.84 minutes, $[M+H]^+$ 449.

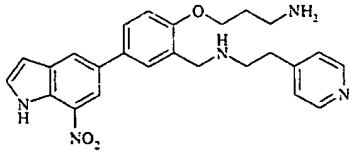
Example 70



As example 68 using 4-(2-aminoethyl)-1N-*t*-butoxycarbonylpiperidine.

LC retention time 2.85 minutes, $[M+H]^+$ 452.

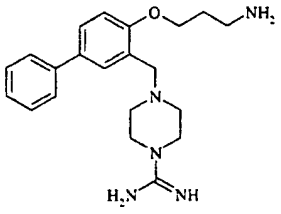
Example 71



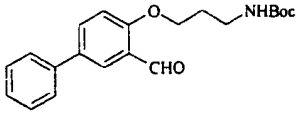
As example 68 using 4-(2-aminoethyl)pyridine.

LC retention time 2.95 minutes, $[M+H]^+$ 446.

Example 72



a)

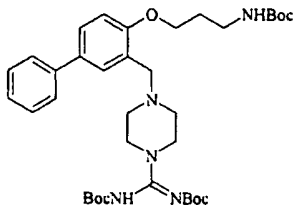


To a mixture of the aldehyde (1 eq) of example 10. dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added phenylboronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 16h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The

organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 4.81 minutes, $[M+Na]^+$ 378.

b)



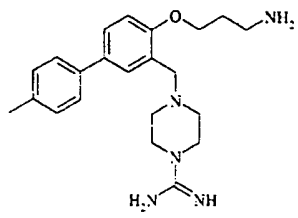
The aldehyde (1 eq) and mono-*N,N'*-bis-*t*-butoxycarbonylpiperazinecarboxamidine (1.6) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of hexane and ethyl acetate.

LC retention time 4.03 minutes, $[M+H]^+$ 668.

c) The tris-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 0.52 and 2.57 minutes, $[M+H]^+$ 368.

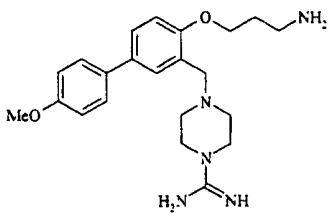
Example 73



As example 72 using *p*-tolylboronic acid.

LC retention time 2.71 minutes, $[M+H]^+$ 382.

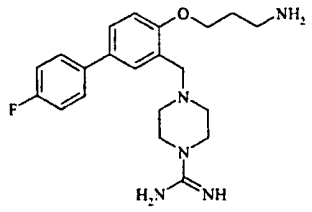
Example 74



As example 72 using 4-methoxyphenylboronic acid.

LC retention time 2.64 minutes, $[M+H]^+$ 398.

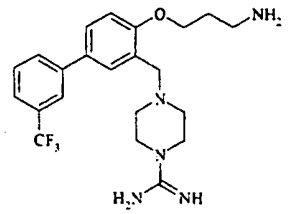
Example 75



As example 72 using 4-fluorophenylboronic acid.

LC retention time 2.63 minutes, $[M+H]^+$ 386.

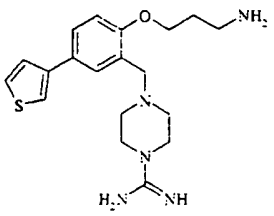
Example 76



As example 72 using 3-trifluoromethylphenylboronic acid.

LC retention time 2.86 minutes. $[M+H]^+$ 436.

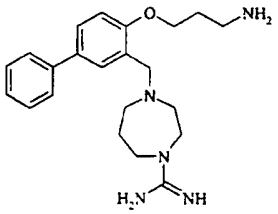
Example 77



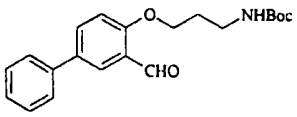
As example 72 using 3-thienylboronic acid.

LC retention time 0.51 and 2.50 minutes, $[M+H]^+$ 374.

Example 78



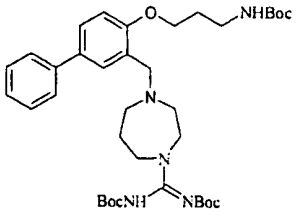
a)



To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added phenylboronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 16h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 4.81 minutes, $[M+Na]^+$ 378.

b)



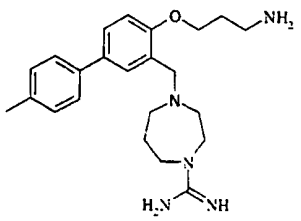
The aldehyde (1 eq) and mono-*N,N'*-bis-*t*-butoxycarbonylhomopiperazinecarboxamidine (1.6 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5 eq) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of hexane and ethyl acetate.

LC retention time 4.03 minutes, $[M+H]^+$ 668.

c) The tris-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 0.50 and 2.46 minutes, $[M+H]^+$ 382.

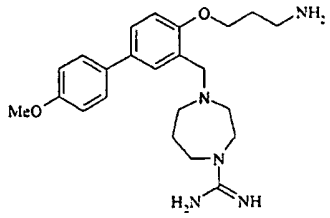
Example 79



As example 78 using *p*-tolylboronic acid.

LC retention time 2.65 minutes. $[M+H]^+$ 396.

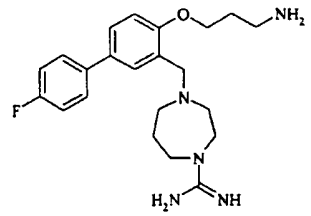
Example 80



As example 78 using 4-methoxyphenylboronic acid.

LC retention time 0.53 and 2.59 minutes, $[M+H]^+$ 412.

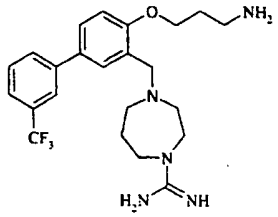
Example 81



As example 78 using 4-fluorophenylboronic acid.

LC retention time 0.54 and 2.56 minutes, $[M+H]^+$ 400.

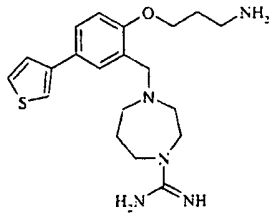
Example 82



As example 78 using 3-trifluoromethylphenylboronic acid.

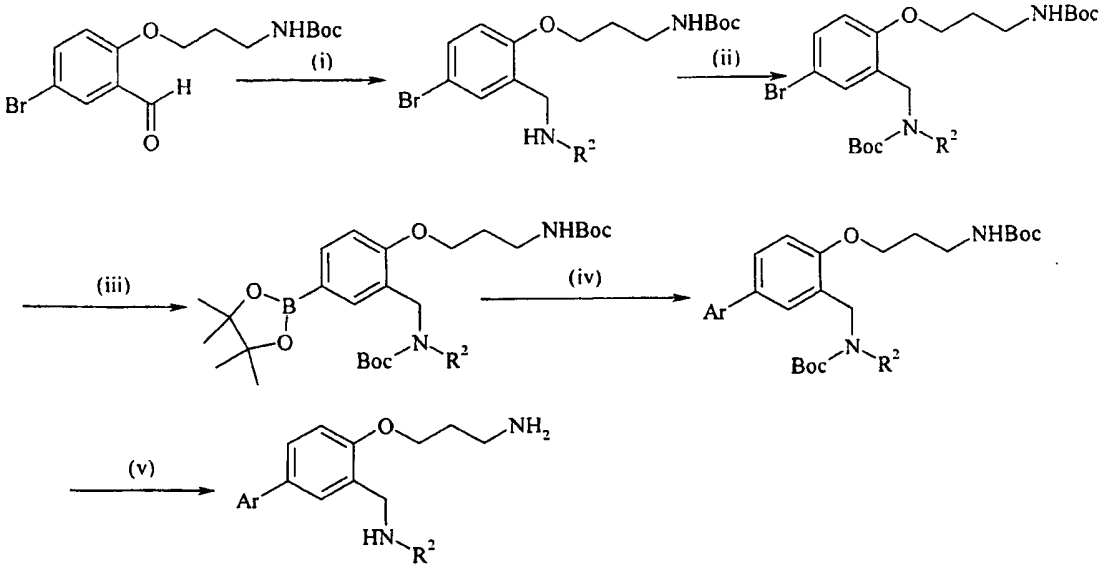
LC retention time 2.78 minutes, $[M+H]^+$ 450.

Example 83



As example 78 using 3-thienylboronic acid.

LC retention time 0.50 and 2.10 minutes, $[M+H]^+$ 388.

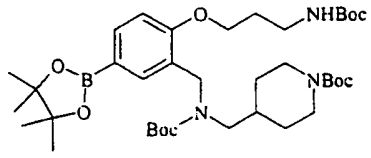


Reagents: (i) R^2NH_2, DCE, sodium triacetoxyborohydride; (ii) Di-t-butyl dicarbonate, DCM, $(i\text{-}Pr)_2NEt$; (iii) Bis(pinacolato)diboron, DMSO, KOAc, $PdCl_2$ $(dppf)_2$; (iv) Arylboronic acid, DMF, K_3PO_4, $PdCl_2$ $(dppf)_2$; (v) TFA/DCM, 1/1.

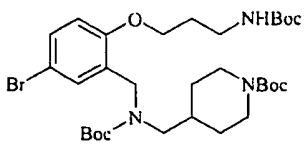
Scheme 4

The following examples were synthesized following the procedure outlined in Scheme 4.

Example 84



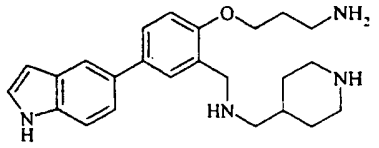
a)



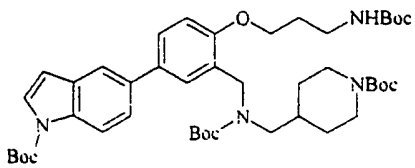
The aldehyde (1eq.) from example 10 and 4-(aminomethyl)-1-Boc-piperidine (1.6eq.) were stirred at RT for 15min in 1,2-dichloroethane. then sodium triacetoxyborohydride (1.5eq.) was added in one portion. After stirring for 16 hours at RT the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was dissolved in DCM and diisopropylethylamine (1eq.) and di-t-butyl dicarbonate (3eq.) added. The reaction was stirred at RT for 1h, diluted with water and the organic layer separated and washed with brine. Drying ($MgSO_4$) and concentration *in vacuo* gave a solid, which was purified by chromatography on silica gel eluting with ethyl acetate/hexane mixtures.
LC retention time 5.41minutes, $[M\text{-}Boc+H]^+$ 556.

b) The bromophenyl compound (1eq.), bis(pinacolato)diboron (1.1eq.) and potassium acetate (3eq.) in DMSO were treated with bis(diphenylphosphino)ferrocene palladium dichloride (10mol %) and heated at 80°C for 3h. After this time, the solvents were partitioned between water and diethylether, the organic layer dried with $MgSO_4$ and finally concentrated. The oil produced was purified using chromatography on silica gel using ethyl acetate/hexanes.
LC retention time 5.45minutes, $[M\text{-}Boc+H]^+$ 604.

Example 85



a)



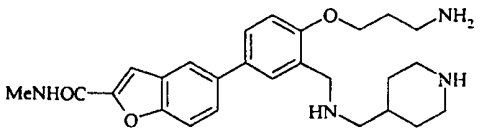
The boronate ester (1eq.) from example 84 was treated with 5-bromo-1-N-Boc-indole (1.5eq.), potassium phosphate (3eq.) and bis(diphenylphosphino)ferrocene palladium dichloride (10 mol%) in DMF at 60°C for 4h. The mixture was filtered through celite and concentrated *in vacuo*. The residue was partitioned between between EtOAc and water, the organic layer was washed with brine and dried ($MgSO_4$). Concentration gave a residue which was purified by column chromatography on silica eluting with ethyl acetate/hexane mixtures.

LC retention time 5.87 minutes, $[M\text{-}Boc+H]^+$ 694.

b)The fully protected compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 2.68 minutes, $[M+H]^+$ 392.

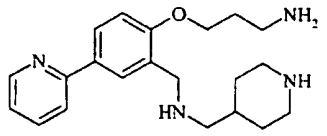
Example 86



As example 85 using 5-bromobenzofuran-2-methylamide.

LC retention time 2.67 minutes, $[M+H]^+$ 451.

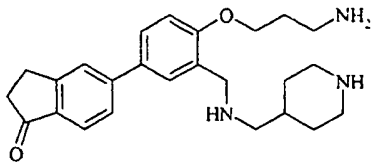
Example 87



As example 85 using 2-bromopyridine.

LC retention time 0.45 minutes. $[M+H]^+$ 355.

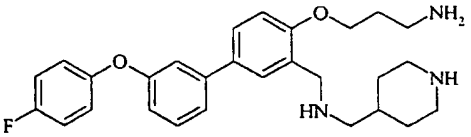
Example 88



As example 85 using 5-bromoindan-2-one.

LC retention time 3.09 minutes, $[M+H]^+$ 408.

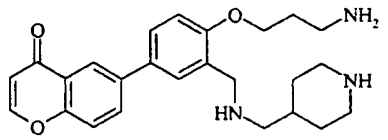
Example 89



As example 85 using 3-bromo(4'-fluoro)diphenylether.

LC retention time 3.24 minutes, $[M+H]^+$ 464.

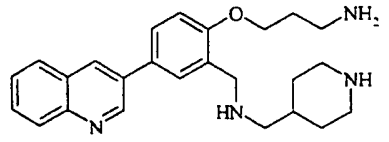
Example 90



As example 85 using 5-bromochromanone.

LC retention time 3.10 minutes, $[M+H]^+$ 422.

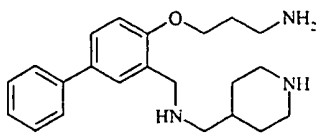
Example 91



As example 85 using 3-bromoquinoline.

LC retention time 3.09 minutes. $[M+H]^+$ 405.

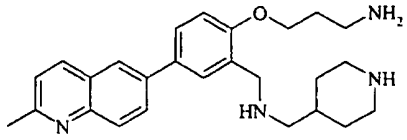
Example 92



As example 85 using bromobenzene.

LC retention time 0.49 minutes, $[M+H]^+$ 354.

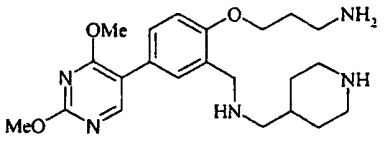
Example 93



As example 85 using 6-bromoquinaldine.

LC retention time 0.47 minutes, $[M+H]^+$ 419.

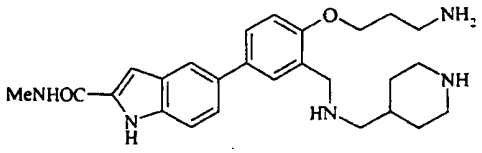
Example 94



As example 85 using 5-bromo-2,4-dimethoxypyrimidine.

LC retention time 3.07 minutes, $[M+H]^+$ 416.

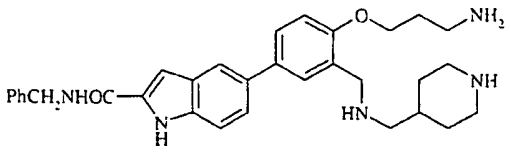
Example 95



As example 85 using 5-bromoindole-2-methylamide.

LC retention time 3.22 minutes, $[M+H]^+$ 450.

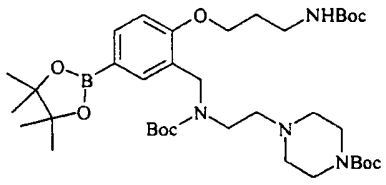
Example 96



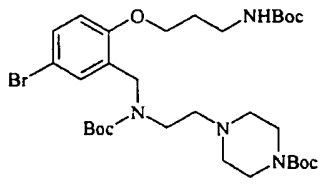
As example 85 using 5-bromoindole-2-benzylamide.

LC retention time 1.11 minutes, $[M+H]^+$ 526.

Example 97



a)



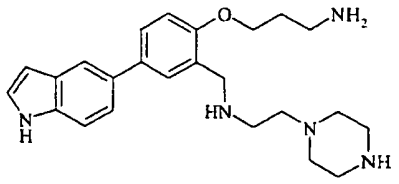
The aldehyde (1eq.) from example 10 and 4-(2-aminomethyl)-1-Boc-piperazine (1.5eq.) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5eq.) was added in one portion. After stirring 16 hours at RT the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid which was dissolved in DCM, and diisopropylethylamine (5eq) and di-t-butyl dicarbonate (2eq.) added. The reaction was stirred at RT for 1h. diluted with water and the organic layer separated and washed with brine. Drying ($MgSO_4$) and concentration *in vacuo* gave a solid which was purified by chromatography on silica gel eluting with ethyl acetate/hexane mixtures.

LC retention time 4.25 minutes. $[M+H]^+$ 673.

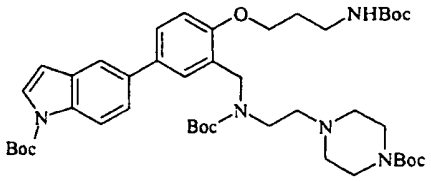
b) The bromophenyl compound (1eq.), bis(pinacolato)diboron (1.1eq.) and potassium acetate (3eq.) in DMSO were treated with bis(diphenylphosphino)ferrocene palladium dichloride (10 mol%) and heated at 80°C for 3h. After this time, the solvents were partitioned between water and diethylether, the organic layer dried with $MgSO_4$ and finally concentrated. The oil produced was purified using chromatography on silica gel using ethyl acetate/hexanes.

LC retention time 4.27 minutes, $[M+H]^+$ 719.

Example 98



a)



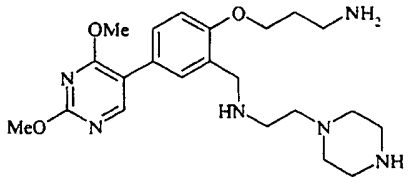
The boronate ester (1eq.) from example 97 was treated with 5-bromo-1-Boc-indole (1.5eq.), potassium phosphate (3eq.) and with bis(diphenylphosphino)ferrocene palladium dichloride (10 mol%) in DMF at 60°C for h. The mixture was filtered through celite and concentrated *in vacuo*. The residue was partitioned between between EtOAc and water, the organic layer was washed with brine and dried ($MgSO_4$). Concentration gave a residue which was purified by column chromatography on silica gel eluting with ethyl acetate/hexane mixtures.

LC retention time 4.79 minutes. $[M+H]^+$ 808.

b) The fully protected compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 2.70 minutes, $[M+H]^+$ 408.

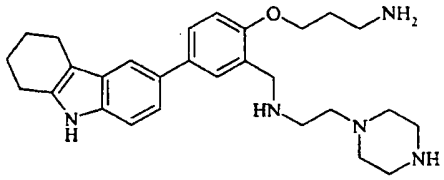
Example 99



As example 98 using 5-bromo-2,4-dimethoxypyrimidine.

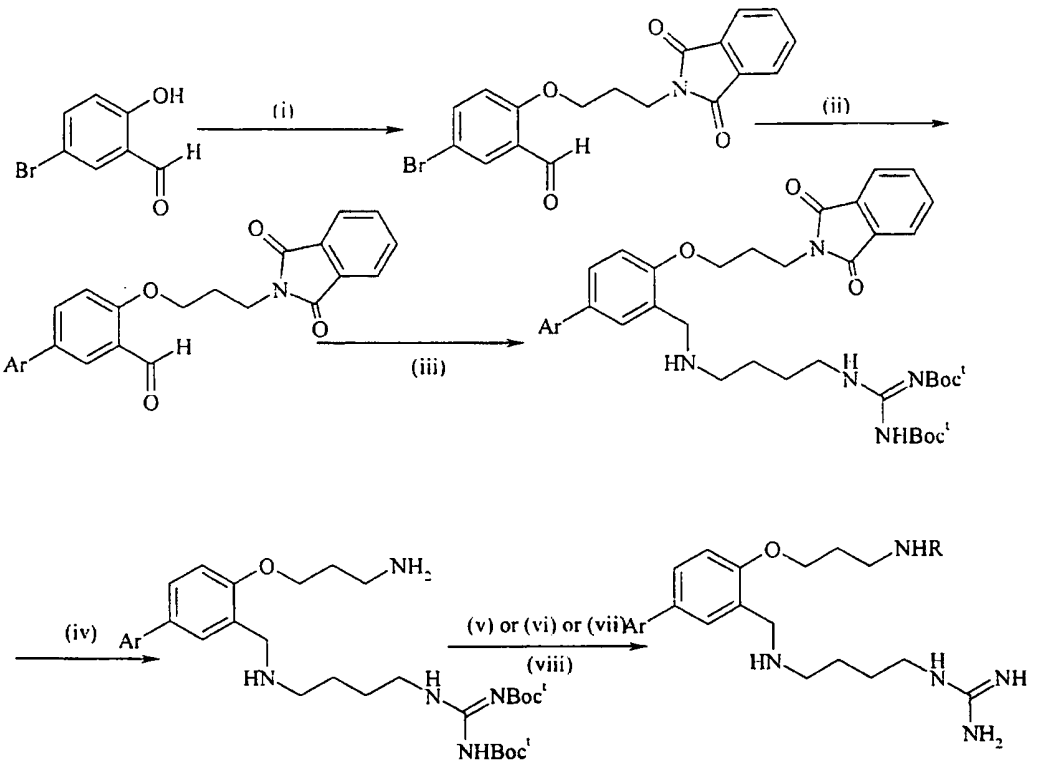
LC retention time 1.03 minutes, $[M+H]^+$ 431.

Example 100



As example 98 using 1,2,3,4-tetrahydro-9-Boc-6-bromocarbazole.

LC retention time 3.21 minutes, $[M+H]^+$ 462.

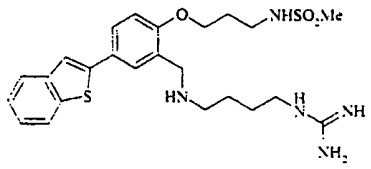


Reagents: (i) 3-bromo-1-phthalamidopropane, Cs_2CO_3, DMF; (ii) 2-Benzo[b]thiopheneboronic acid, DME, K_2CO_3; (iii) (a) (*N,N'*-bis-butoxycarbonyl)$NH(CH_2)_4NH_2$, DCE, sodium triacetoxyborohydride, (b) di-t-butyl dicarbonate, DCM, $(i\text{-}Pr)_2NEt$; (iv) hydrazine.hydrate, ; (v) RSO_2Cl, Et_3N, DCM; (vi) RCOCl, Et_3N, CH_3CN; (vii) RCl (R=heterocycle), $(i\text{-}Pr)_2NEt$, ; (viii) TFA/DCM, 1/1.

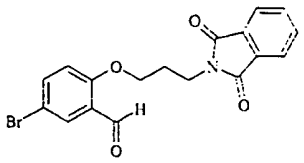
Scheme 5

The following examples were synthesized following the procedure outlined in Scheme 5.

Example 101.



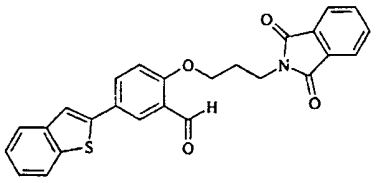
a)



5-Bromosalicylaldehyde (1 eq.) and cesium carbonate (2 eq.) were stirred in DMF and 3-bromo-1-phthalamidopropane (1.2 eq.) was added. After stirring for 18 hours at room temperature the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc and water and the organic layer washed with brine. Drying ($MgSO_4$) and concentration gave a residue which was purified by column chromatography on silica eluting with EtOAc/hexane to yield the protected amine.

LC retention time 4.69 minutes, $[M]^+$ 388.

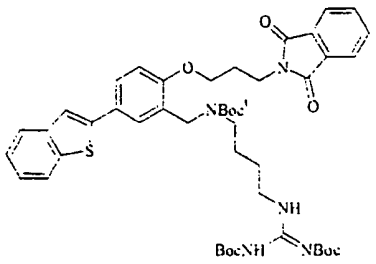
b)



To the aldehyde (1 eq.), 2N K_2CO_3 and benzo[b]thiophene-2-boronic acid (2 eq.) in dry, degassed DME was added dichlorobis(triphenylphosphine)palladium (0.1 eq.), and the mixture heated at 80°C for 18 h. After this time the reaction mixture was filtered, concentrated *in vacuo*, re-dissolved in ethyl acetate and washed with water and saturated sodium chloride solution. The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*.

LC retention time 5.24 minutes, $[M+H]^+$ 442.

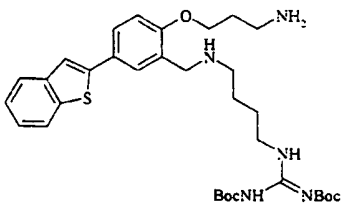
c)



The aldehyde (1 eq.) and 1-amino-4-*N,N'*-bis-Boc-guanidinobutane (1.5 eq.) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5 eq.) was added in one portion. After stirring for 18 hours at RT the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid which was dissolved in DCM and treated with diisopropylethylamine (2 eq.) and di-t-butyl dicarbonate (2 eq.). After stirring for 4h at RT the reaction was diluted with water, the organic layer was washed with brine, and dried over $MgSO_4$. Concentration gave a solid which was purified by chromatography on silica gel eluting with 4:1 hexane:ethyl acetate, then 2:1 hexane:ethyl acetate

LC retention time 5.95 minutes, $[M+H]^+$ 856.4

d)



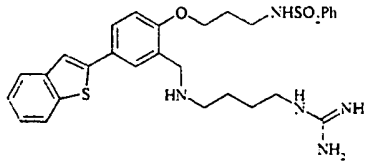
The *N*-protected phthalimide (1 eq.) was treated with hydrazine hydrate (15 eq.) in EtOH for 18 h then concentrated *in vacuo* keeping the water bath below 40°C. The residue was dissolved in EtOAc and the organic layer washed exhaustively with water and finally with brine. The organic fraction was dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography on silica, eluting with 75%EtOAc/hexane, then 5%MeOH/DCM.

e) The amine (1 eq.) and triethylamine (5 eq.) in acetonitrile was treated with methanesulfonyl chloride (3 eq.). After 2h at RT the reaction was diluted with water and the organic layer separated, washed with brine and dried ($MgSO_4$). Concentration gave an oil which was purified by column chromatography on silica, eluting with 1:1 EtOAc/hexane to yield the desired methane sulfonate.

The bis-Boc compound was treated with 1 mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired mono-guanidine as the bis-trifluoroacetate.

LC retention time 3.19 minutes, $[M+H]^+$ 504.

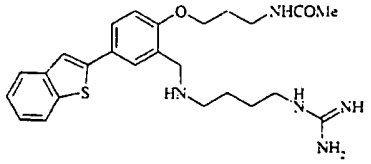
Example 102.



As example 101 using benzenesulfonyl chloride.

LC retention time 3.35 minutes, $[M+H]^+$ 566.

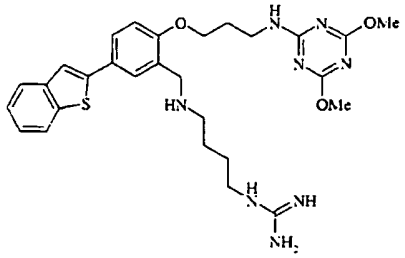
Example 103.



As example 101 using acetyl chloride.

LC retention time 3.12 minutes, $[M+H]^+$ 468.

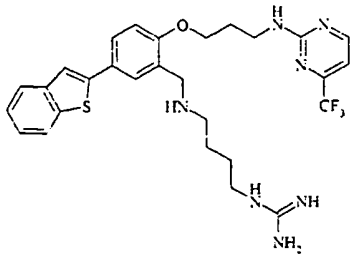
Example 104.



As example 101 using 2-chloro-4,6-dimethoxytriazine.

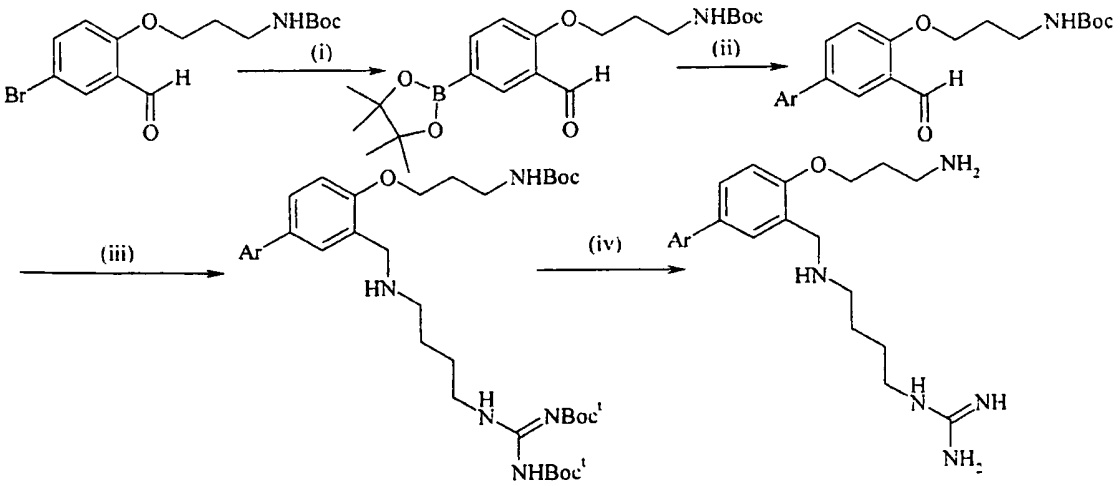
LC retention time 3.24 minutes. $[M+H]^+$ 565.

Example 105.



As example 101 using 2-chloro-4-trifluoromethylpyrimidine.

LC retention time 3.45 minutes, $[M+H]^+$ 518.

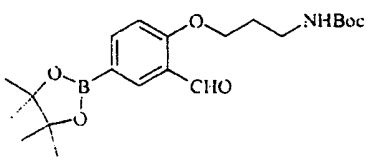


Reagents: (i) Bis(pinacolato)diboron, KOAc, DMSO, $PdCl_2$ $(dppf)_2$; (ii) Arylboronic acid, DMF, K_3PO_4, $PdCl_2$ $(dppf)_2$; (iii) (N,N'-bis-t-butoxycarbonyl)$NH(CH_2)_3CH_2NH_2$, DCE, sodium triacetoxyborohydride; (iv) TFA/DCM, 1/1.

Scheme 6

The following examples were synthesized following the procedure outlined in Scheme 6.

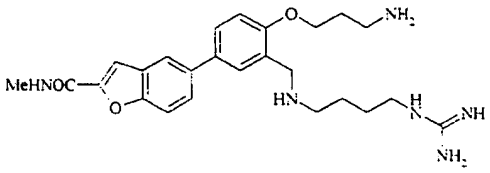
Example 106



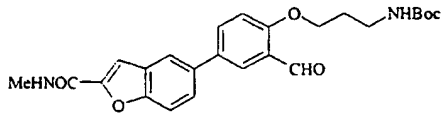
The aldehyde (1eq.) from example 10, bis(pinacolato)diboron (1.1eq.) and potassium acetate (3eq.) in DMSO were treated with bis(diphenylphosphino)ferrocene palladium dichloride (10 mol%) and heated at 80°C for 3h. After this time, the solvents were partitioned between water and diethylether, the organic layer dried with $MgSO_4$ and finally concentrated. The oil produced was purified using chromatography on silica gel using ethyl acetate/hexanes.

LC retention time 4.81 minutes, $[M\text{-}Boc+H]^+$ 306.

Example 107



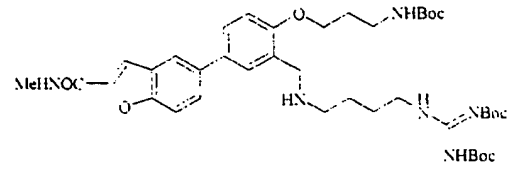
a)



The boronate ester (1eq.) from example 106 was treated with 5-bromobenzofuran-2-methylamide (1.5eq.), potassium phosphate (3eq.) and bis(diphenylphosphino)ferrocene palladium dichloride (10 mol%) in DMF at 60°C for 3h. The mixture was filtered through celite and concentrated *in vacuo*. The residue was partitioned between between EtOAc and water, the organic layer was washed with brine and dried (MgSO4). Concentration gave a residue which was purified by column chromatography on silica eluting with ethyl acetate/hexane mixtures.

LC retention time 4.89 minutes, $[M\text{-}Boc+H]^+$ 429.

b)



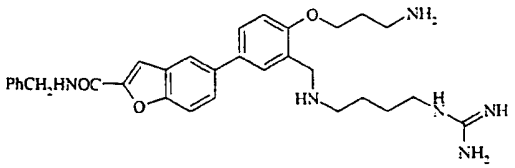
The aldehyde (1eq.) and 1-amino-4-(N,N'bis-Boc-guanidino)butane (1.5eq.) were stirred at RT for 15min in dichloroethane, then sodium triacetoxyborohydride (1.5eq.) was added in one portion. After stirring 16 hours at RT the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid which was purified by chromatography on silica gel eluting with ethyl acetate/hexane mixtures.

LC retention time 4.40 minutes, $[M\text{-}Boc+H]^+$ 667.

c) The tris-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 1h. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 3.17 minutes, $[M+H]^+$ 467.

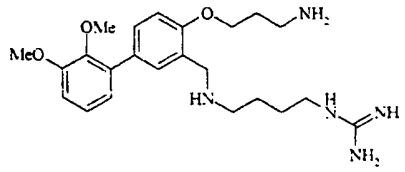
Example 108



As example 107 using 5-bromobenzofuran-2-benzylamide.

LC retention time 3.19 minutes, $[M+H]^+$ 543.

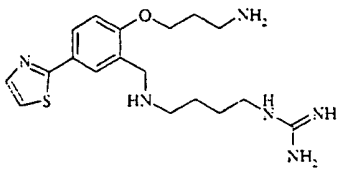
Example 109



As example 107 using 1-bromo-2,3-dimethoxybenzene.

LC retention time 3.10 minutes. $[M+H]^+$ 430.

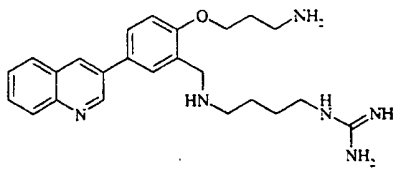
Example 110



As example 107 using 2-bromothiazole.

LC retention time 1.06 minutes, $[M+H]^+$ 377.

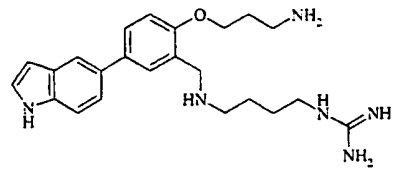
Example 111



As example 107 using 3-bromoquinoline.

LC retention time 3.13 minutes, $[M+H]^+$ 421.

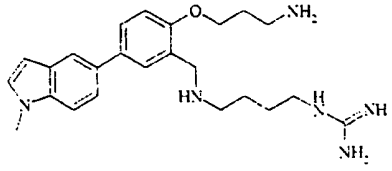
Example 112



As example 107 using 5-bromo-1-butoxycarbonylindole.

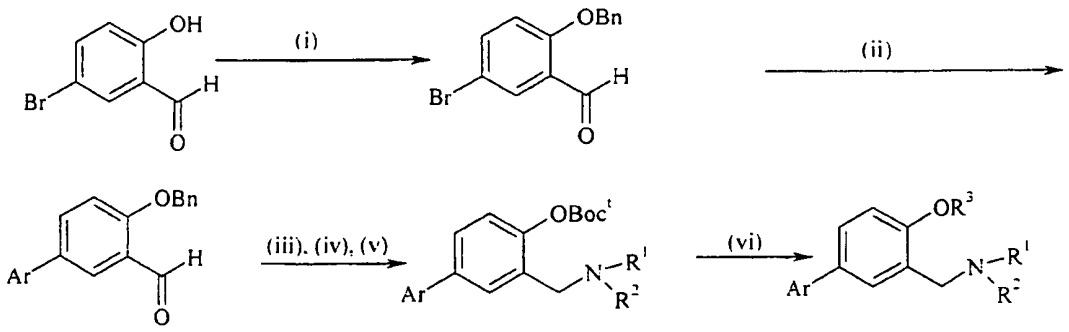
LC retention time 3.13 minutes, $[M+H]^+$ 409.

Example 113



As example 107 using 5-bromo-1-methylindole.

LC retention time 2.77 minutes. $[M+H]^-$ 423.

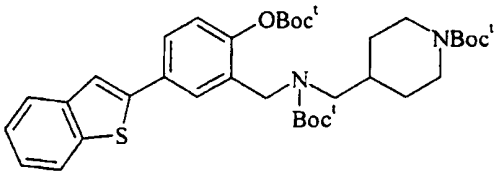


Reagents: (i) BnBr, Cs_2CO_3, DMF ; (ii) $ArB(OH)_2$, DME, K_2CO_3, $PdCl_2(PPh_3)_2$; (iii) $BCl_3 \cdot SMe_2$, DCM; (iv) R_1R_2NH, MeOH-CH_2Cl_2 (1:1 v/v), Amberlyst A-26 borohydride resin; (v) Boc_2O, DIPEA, MeCN; (vi) EtOH, Cs_2CO_3, then R^3X, DMF.

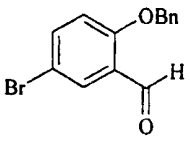
Scheme 7

The following examples were synthesised following the procedure outlined in scheme 7.

Example 114.

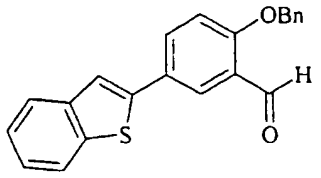


a)



To 5-bromosalicaldehyde (1 eq.) and Cs_2CO_3 (2 eq.) in DMF was added benzyl bromide (1.1 eq.), and the solution stirred under nitrogen for 24 hours. The mixture was poured into water and extracted with ethyl acetate. The organic fraction was washed with water and saturated sodium chloride solution, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the benzyl ether as a white solid.

b)



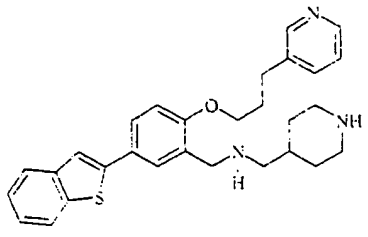
To the aryl bromide (1 eq.), 2N K_2CO_3 and benzo[b]thiophene-2-boronic acid (2 eq.) in dry, degassed DME was added dichlorobis(triphenylphosphine)palladium(II) (0.1 eq.) and the mixture heated at 80°C for 45 hours. After this time the reaction mixture was filtered, concentrated *in vacuo*, re-dissolved in ethyl acetate and washed with water and saturated sodium chloride solution. The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*.

LC retention time 5.47 minutes, $[M+H]^+$ 345.

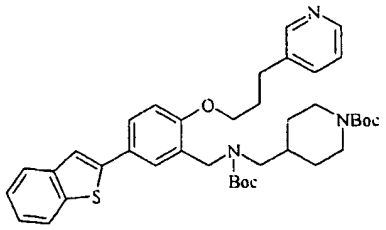
c) The bisaryl (example 114b, 1 eq.) and boron trichloride-methyl sulfide complex (2 eq.) were stirred in dichloromethane for one hour. Saturated sodium bicarbonate was added and the organics collected. After passing through a short pad of silica and concentration under reduced pressure, the product was suspended in methanol-dichloromethane (1:1 v/v) and shaken with 4-(aminomethyl)piperidine (1 eq.). After one hour, borohydride (solid supported upon Amberlyst A-26 resin, 1.1 eq.) was added and shaking continued for 18 hours. After filtration, the solution was concentrated under reduced pressure, re-dissolved in acetonitrile and stirred for 18 hours with di-t-butyl dicarbonate (2 eq.) and di-isopropylethylamine (2 eq.). The resultant mixture was poured into water and extracted with ethyl acetate. After concentration *in vacuo*, the compound was purified by chromatography on silica gel, eluting with hexanes and ethyl acetate (4:1 v/v)

LC retention time 5.68 minutes.

Example 115



a)

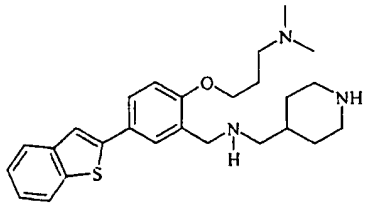


The bisaryl (example 114, 1 eq.) and Cs_2CO_3 (2 eq.) in ethanol were heated to 80°C for one hour, and then concentrated to dryness. After re-suspension in DMF and warming to 45°C under nitrogen, 3-(3-pyridyl)-1-bromopropane (1.5 eq.) was added and the suspension stirred for 18 hours. After concentration *in vacuo*, the compound was purified by chromatography on silica gel, eluting with hexane:ethyl acetate (2:1 v/v), then dichloromethane:methanol (9:1 v/v).

b) The thus purified fully protected compound was treated with 1 mL of 1/1 TFA/DCM and stirred at RT for 30 minutes. The volatiles were removed under reduced pressure to give the desired diamine as the tris-trifluoroacetate.

LC retention time 3.02 minutes, $[M+H]^+$ 472.

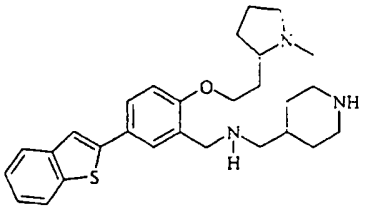
Example 116.



As example 115 using 1-chloro-3-(N,N-dimethylamino)propane.

LC retention time 3.02 minutes. $[M+H]^+$ 438.

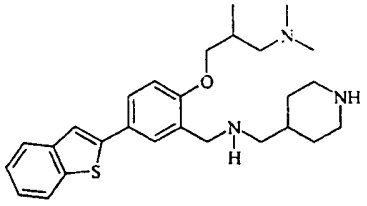
Example 117.



As example 115 using 2-(2-chloroethyl)-1-methylpyrrolidine.

LC retention time 3.00 minutes, $[M+H]^+$ 464.

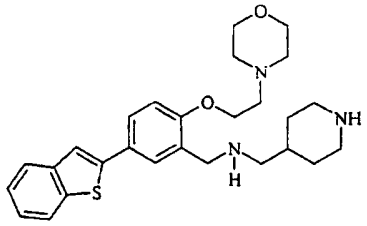
Example 118.



As example 115 using 1-chloro-3-(N,N-dimethylamino)-2-methylpropane.

LC retention time 3.16 minutes, $[M+H]^+$ 452.

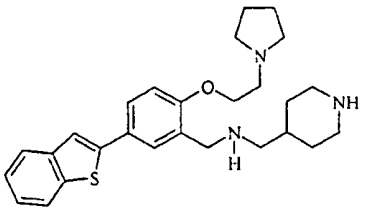
Example 119.



As example 115 using 4-(2-chloroethyl)morpholine.

LC retention time 3.17 minutes, $[M+H]^+$ 466.

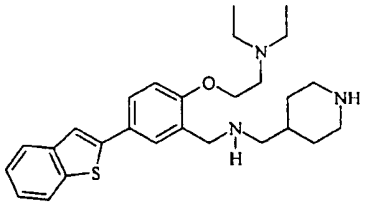
Example 120.



As example 115 using N-(2-chloroethyl)pyrrolidine.

LC retention time 3.16 minutes, $[M+H]^+$ 450.

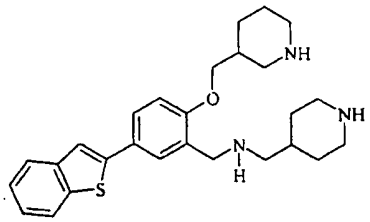
Example 121.



As example 115 using 2-bromoethyl-*N,N*-diethylamine.

LC retention time 3.20 minutes, $[M+H]^+$ 452.

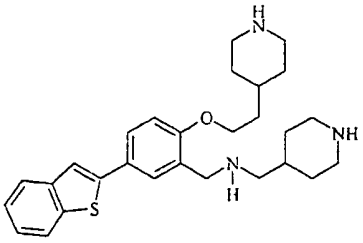
Example 122.



As example 115 using *N*-Boc^t-3-(bromomethyl)piperidine.

LC retention time 3.24 minutes, $[M+H]^+$ 450.

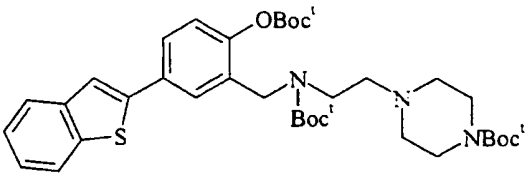
Example 123.



As example 115 using *N*-Boc^t-4-(2-bromoethyl)piperidine.

LC retention time 3.24 minutes, $[M+H]^+$ 464.

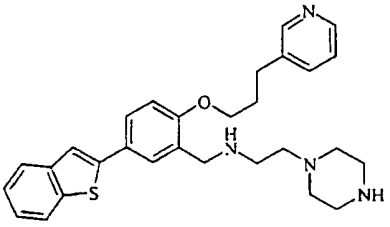
Example 124



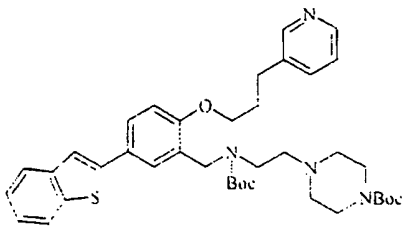
As example 114 using *N*-(2-aminoethyl)piperidine.

LC retention time 4.75 minutes, $[M+H]^+$ 668.

Example 125.



a)

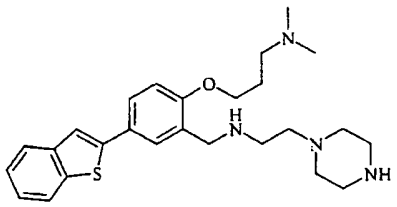


The bisaryl (example 124, 1 eq.) and Cs_2CO_3 (2 eq.) in ethanol were heated to 80°C for one hour, and then concentrated to dryness. After re-suspension in DMF and warming to 45°C under nitrogen, 3-(3-pyridyl)-1-bromopropane (1.5 eq.) was added and the suspension stirred for 18 hours. After concentration *in vacuo*, the compound was purified by chromatography on silica gel, eluting with hexane:ethyl acetate (2:1 v/v), then dichloromethane:methanol (9:1 v/v).

b) The thus purified fully protected compound was treated with 1 mL of 1/1 TFA/DCM and stirred at RT for 30 minutes. The volatiles were removed under reduced pressure to give the desired triamine as the tetrakis-trifluoroacetate.

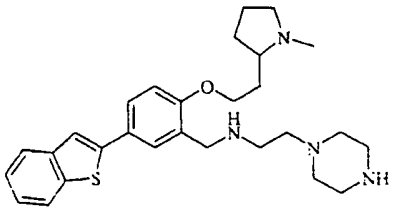
LC retention time 3.09 minutes, $[M+H]^+$ 487.

Example 126.



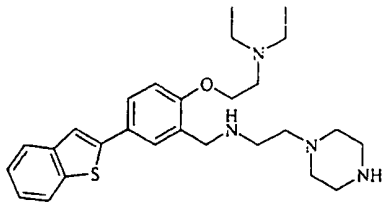
As example 125 using 1-chloro-3-(N,N-dimethylamino)propane
LC retention time 2.91 minutes, $[M+H]^+$ 453.

Example 127.



As example 125 using 2-(2-chloroethyl)-1-methylpyrrolidine.
LC retention time 2.97 minutes. $[M+H]^+$ 479.

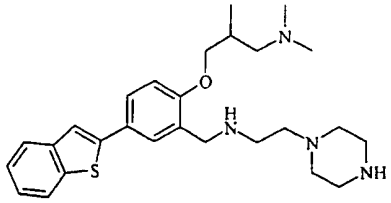
Example 128.



As example 125 using 2-bromoethyl-N,N-diethylamine.

LC retention time 3.21 minutes, $[M+H]^+$ 467.

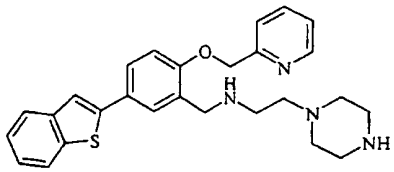
Example 129.



As example 125 using 1-chloro-3-(N,N-dimethylamino)-2-methylpropane.

LC retention time 3.21 minutes, $[M+H]^+$ 467.

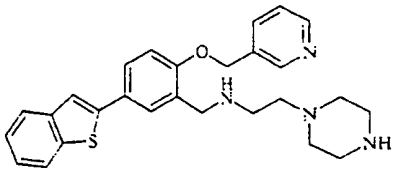
Example 130.



As example 125 using 2-picolyl chloride.

LC retention time 3.30 minutes, $[M+H]^+$ 459.

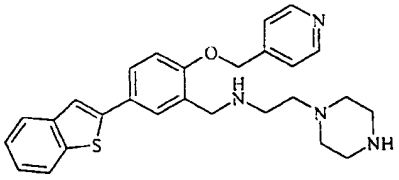
Example 131.



As example 125 using 3-picolyl chloride.

LC retention time 3.27 minutes. $[M+H]^+$ 459.

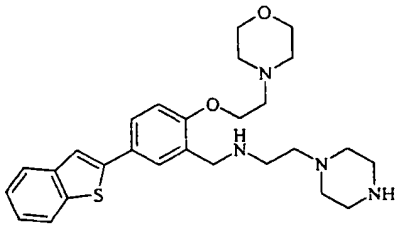
Example 132.



As example 125 using 4-picolyl chloride.

LC retention time 3.26 minutes, $[M+H]^+$ 459.

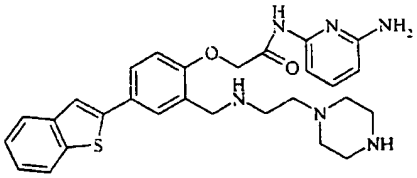
Example 133.



As example 125 using 4-(2-chloroethyl)morpholine.

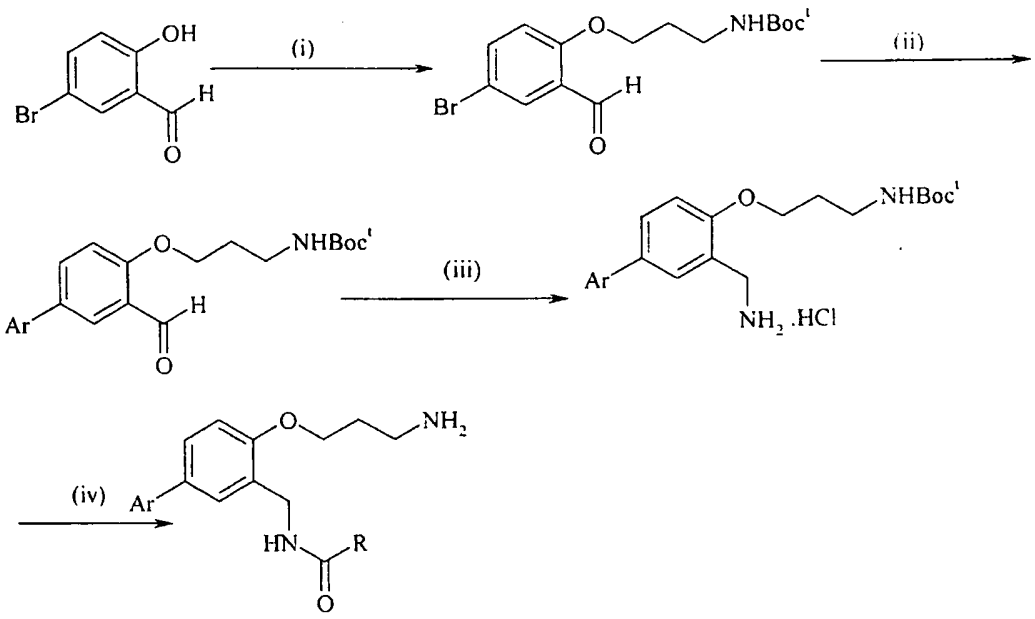
LC retention time 3.18 minutes, $[M+H]^+$ 481.

Example 134.



As example 125 using 2-amino-6-(bromoethanoylamino)pyridine.

LC retention time 3.34 minutes. $[M+H]^+$ 517.

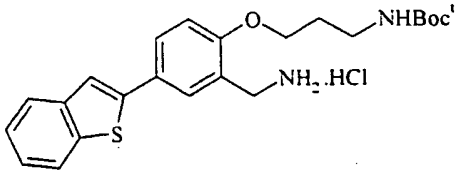


Reagents: (i) *N*-Boc-bromopropylamine, Cs_2CO_3, DMF; (ii) 2-Benzo[b]thiopheneboronic acid, DME, $PdCl_2(PPh_3)_2$, K_2CO_3; (iii) (a) $NH_2OH.HCl$, Et_3N, 1,2-DCE, (b) H_2, 10%Pd/C, MeOH, $CHCl_3$; (iv) (a) RCO_2H, HBTU, TEA, (b) TFA/DCM, 1/1.

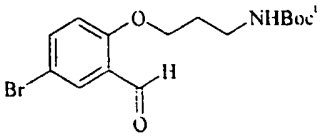
Scheme 8

The following examples were synthesised following the procedure outlined in scheme 8.

Example 135.



a)

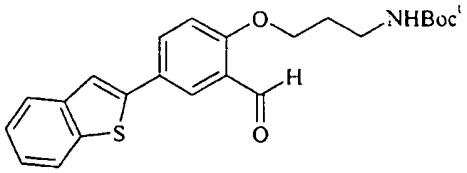


To 5-bromosalicaldehyde (1 eq.) and Cs_2CO_3 (2 eq.) in DMF was added Boc-3-bromopropylamine (1.2 eq.), and the solution stirred under nitrogen for 24 hours. The

mixture was poured into water and extracted with ethyl acetate. The organic fraction was washed with water and saturated sodium chloride solution, dried and concentrated *in vacuo* to give the ether as a white solid.

LC retention time 4.68 minutes, $[M+H]^+$ 380.

b)



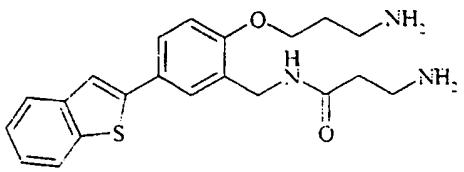
To the aryl bromide (1 eq.), 2N K_2CO_3 and benzo[b]thiophene-2-boronic acid (2 eq.) in dry, degassed DME was added dichlorobis(triphenylphosphine)palladium(II) (0.1 eq.) and the mixture heated at 80°C for 45 hours. After this time the reaction mixture was filtered, concentrated *in vacuo*, re-dissolved in ethyl acetate and washed with water and saturated sodium chloride solution. The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*.

LC retention time 5.19 minutes, $[M\text{-}Boc^t+H]^+$ 298.

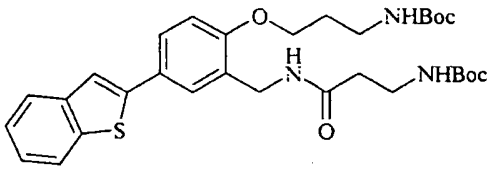
c) The aldehyde (1 eq.), hydroxylamine hydrochloride (1.5 eq.) and triethylamine (2 eq.) were stirred for 18 hours in 1,2-dichloroethane. The mixture was then poured into dichloromethane and washed with brine. The organic fraction was dried, filtered and concentrated under reduced pressure. The resultant compound was re-dissolved in methanol, a few drops of chloroform were added, and the mixture stirred under a hydrogen atmosphere for 18 hours over 10% palladium on carbon (1 eq. by weight). After filtration through a short pad of celite, the volatiles were removed under reduced pressure to give the amine as the hydrochloride salt.

LC retention time 3.75 minutes, $[M+H]^+$ 413.

Example 136.



a)

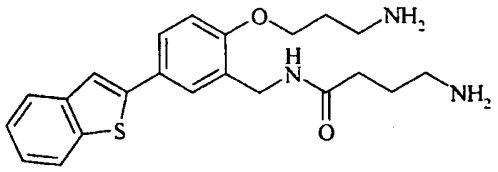


The amine from example 135, Boc-3-aminopropanoic acid (1 eq.), hydroxybenzotriazole (1.1 eq.) and triethylamine (5 eq.) were stirred together in DMF for 18 hours. The reaction mixture was concentrated *in vacuo* and partitioned between EtOAc and water and the organic layer dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica eluting with 75%EtOAc/hexane.

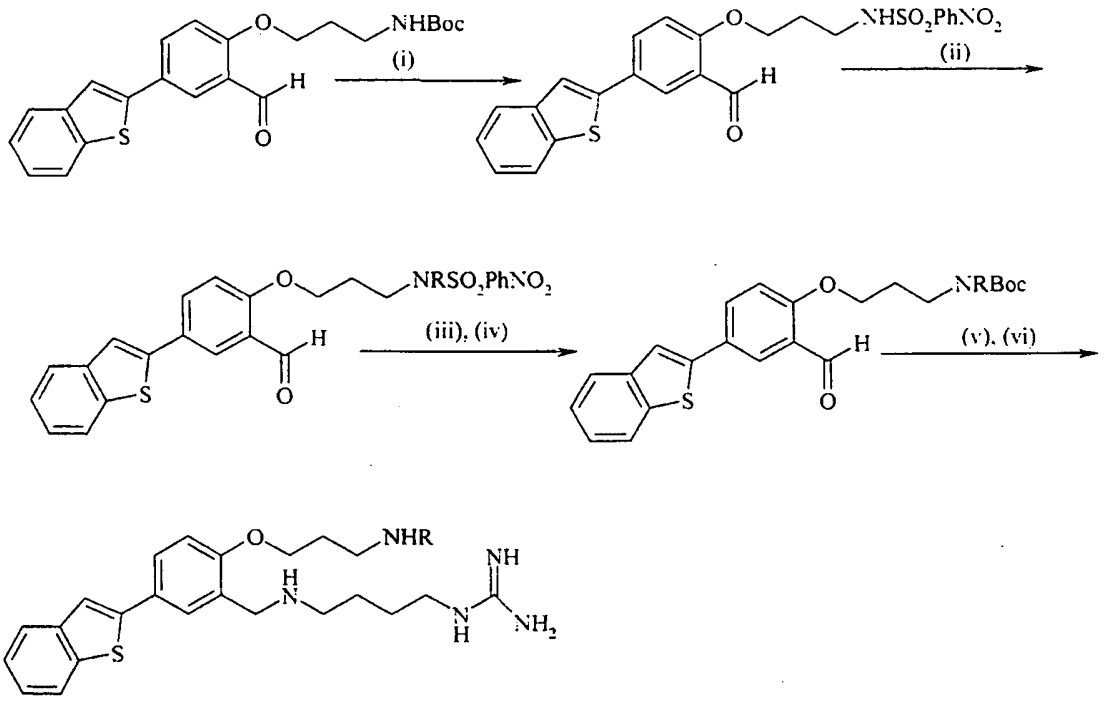
LC retention time 5.05 minutes, $[M+H]^+$ 570.

b) The thus purified fully protected compound was treated with 1 mL of 1/1 TFA/DCM and stirred at RT for 30 minutes. The volatiles were removed under reduced pressure to give the desired diamine as the bistrifluoroacetate.

Example 137.



As for example 136, using N-Boc-4-aminobutanoic acid.

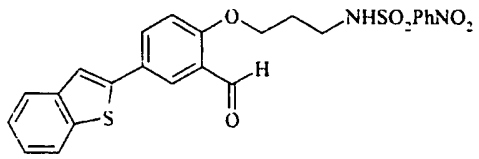


Reagents: (i) (a) TFA/DCM, (b) 2-Nitro-phenylsulfonyl chloride, TEA, DCM; (ii) RX, Cs_2CO_3, DMF; (iii) PhSH, DBU, CH_3CN; (iv) Boc_2O, DIPEA, CH_3CN; (v) 1-amino-4-(*N,N'*-bis-Bocguanidino)butane, $NaB(OAc)_3H$, 1,2-DCE; (vi)TFA/DCM, 1/1.

Scheme 9

The following examples were synthesised following the procedure outlined in scheme 9.

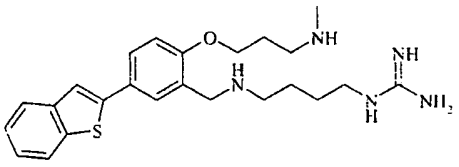
Example 138.



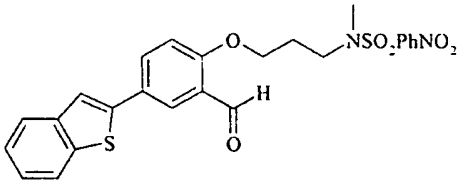
The aldehyde from example 25 (1 eq.), was dissolved in 1 mL of 1/1 TFA/DCM and stirred at RT for 30 minutes. The volatiles were removed under reduced pressure to give the amine as the trifluoroacetate salt. This salt was re-dissolved in dichloromethane and

stirred with 2-nitrophenylsulfonyl chloride (2 eq.) and triethylamine (2 eq.) for 2 hours. The mixture was poured into water and extracted with ethyl acetate. The organic fraction was washed with water and saturated sodium chloride solution, dried ($MgSO_4$) and concentrated under reduced pressure to give the sulfonamide as a white solid.

Example 139

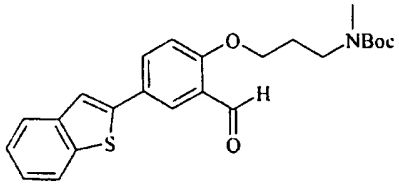


a)



To the aldehyde from example 138 (1 eq.), and Cs_2CO_3 (2 eq.) in DMF was added methyl iodide (2 eq.), and the solution stirred under nitrogen for 24 hours. The mixture was poured into water and extracted with ethyl acetate. The organic fraction was washed with water and saturated sodium chloride solution, dried and concentrated under reduced pressure.

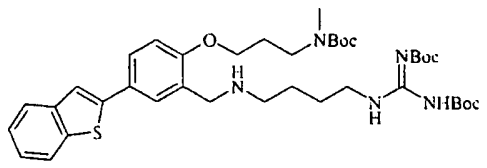
b)



The biaryl (1 eq.), DBU (5 eq.) and thiophenol (4 eq.) were stirred together in DMF for 2h hours. The mixture was concentrated *in vacuo* and partitioned between EtOAc and water, the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. The compound was then re-dissolved in acetonitrile and stirred for 18 hours with di-^{t}butyl dicarbonate (2 eq.) and di-isopropylethylamine (2 eq.). The resultant mixture was poured into water and extracted

with ethyl acetate. The organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the desired compound.

c)

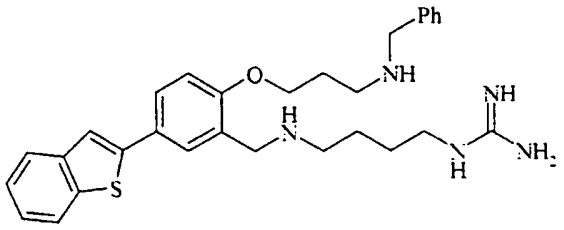


The aldehyde (1 eq.) and 1-amino-4-(N,N'bis-Boc-guanidino)butane (1.5 eq.) were stirred at RT for 15min in dichloroethane, then sodium triacetoxyborohydride (1.5 eq.) was added. After stirring for 18 hours at RT the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc and water. The organic layer was dried, filtered and concentrated *in vacuo* to give the crude product. This was purified by column chromatography (silica, eluting with dichloromethane, then dichloromethane: methanol 95:5 v/v).

d) The thus purified fully protected compound was treated with 1 mL of 1/1 TFA/DCM and stirred at RT for 30 minutes. The volatiles were removed *in vacuo* to give the desired guanidine as the tris-trifluoroacetate.

LC retention time 2.88 minutes. $[M+H]^+$ 440.

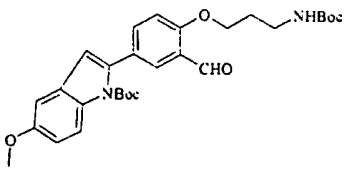
Example 140.



As for example 139. using benzyl bromide.

LC retention time 3.054 minutes. $[M+H]^+$ 516.25.

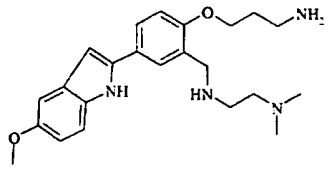
Example 141



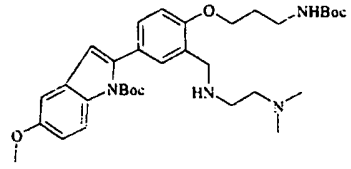
To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added 5-methoxyindole-2-boronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 1h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.19 minutes, $[M+H\text{-}Boc]^+$ 425.

Example 142



a)

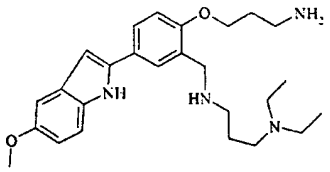


The aldehyde (1 eq) from example 141 and N,N-Dimethylethylenediamine (1.6 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was

washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.
LC retention time 3.65 minutes, $[M+H]^+$ 567.

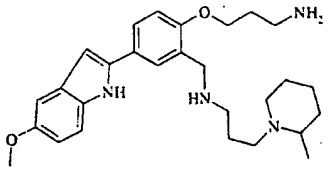
b) The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10 min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.
LC retention time 2.81 minutes, $[M+H]^+$ 397.

Example 143



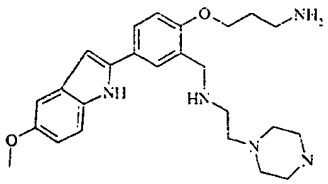
As example 142 using N,N-Diethylpropylenediamine.
LC retention time 2.80 minutes, $[M+H]^+$ 439.

Example 144



As example 142 using 1-(3-Aminopropyl)-2-pipecoline.
LC retention time 2.88 minutes, $[M+H]^+$ 465.

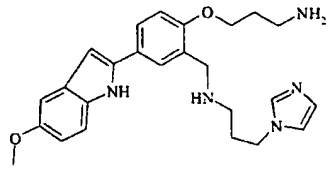
Example 145



As example 142 using 1-(2-Aminoethyl)piperazine.

LC retention time 2.82 minutes, $[M+H]^+$ 438.

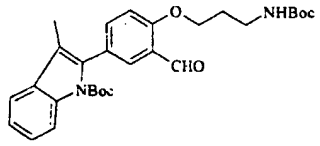
Example 146



As example 142 using 1-(3-Aminopropyl)imidazole.

LC retention time 2.78 minutes, $[M+H]^+$ 434.

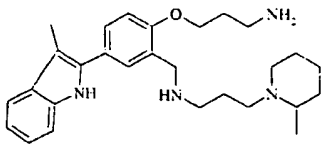
Example 147



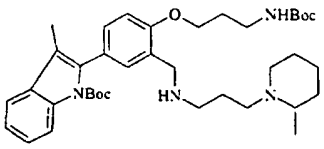
To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added 3-methylindole-2-boronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 1h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.33 minutes, $[M+H\text{-}Boc]^+$ 409.

Example 148



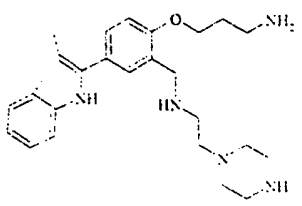
a)



The aldehyde (1 eq) from example 147 and 1-(3-Aminopropyl)-2-pipecoline (1.6 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.
LC retention time 3.65 minutes, $[M+H]^+$ 649.

b) The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10 min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.
LC retention time 2.94 minutes, $[M+H]^+$ 449.

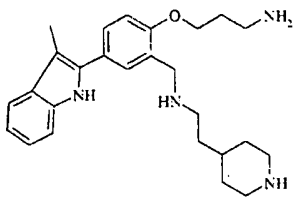
Example 149



As example 148 using 1-(2-Aminoethyl)piperazine.

LC retention time 2.88 minutes, $[M+H]^+$ 422.

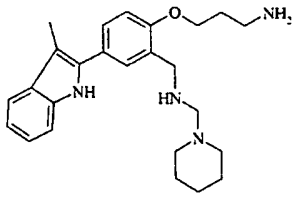
Example 150



As example 148 using 1-(2-Aminoethyl)piperidine.

LC retention time 2.90 minutes, $[M+H]^+$ 421.

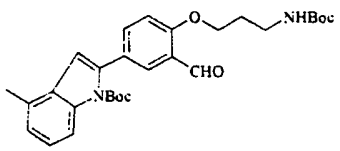
Example 151



As example 148 using 4-(Aminomethyl)piperidine.

LC retention time 3.58 minutes, $[M+H]^+$ 406.

Example 152

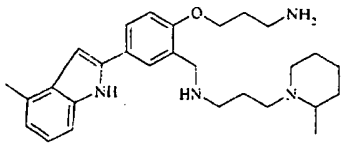


To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added 4-methylindole-2-boronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 1h. After cooling to RT the

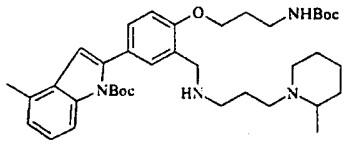
solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.28 minutes, $[M+H-Boc]^+$ 409.

Example 153



a)



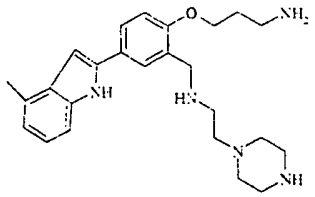
The aldehyde (1 eq) from example 152 and 1-(3-Aminopropyl)-2-pipecoline (1.6 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.

LC retention time 3.66 minutes, $[M+H]^+$ 649.

b) The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10 min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.

LC retention time 2.92 minutes. $[M+H]^+$ 449.

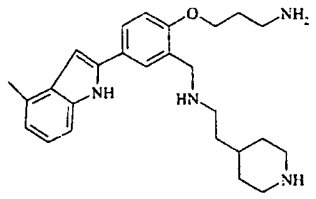
Example 154



As example 153 using 1-(2-Aminoethyl)piperazine.

LC retention time 2.86 minutes, $[M+H]^+$ 422.

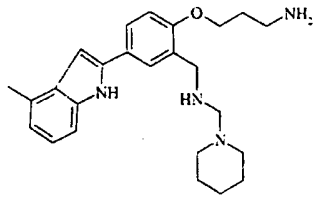
Example 155



As example 153 using 1-(2-Aminoethyl)piperidine.

LC retention time 2.92 minutes, $[M+H]^+$ 421.

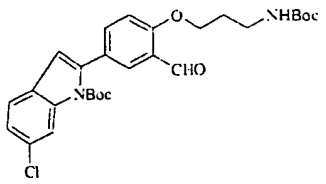
Example 156



As example 153 using 4-(Aminomethyl)piperidine.

LC retention time 2.91 minutes. $[M+H]^+$ 407.

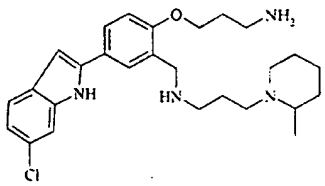
Example 157



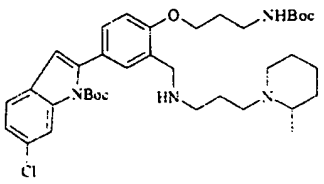
To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added 6-chloroindole-2-boronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 1h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.16 minutes, $[M+H-Boc]^+$ 429.

Example 158



a)

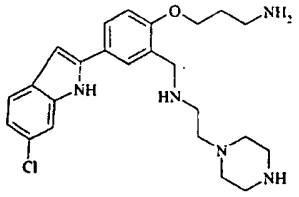


The aldehyde (1 eq) from example 157 and 1-(3-Aminopropyl)-2-pipecoline (1.6 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was

washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.
LC retention time 3.73 minutes, $[M+H]^+$ 669.

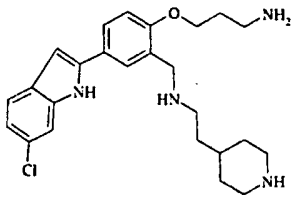
b) The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10 min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.
LC retention time 3.04 minutes. $[M+H]^+$ 469.

Example 159



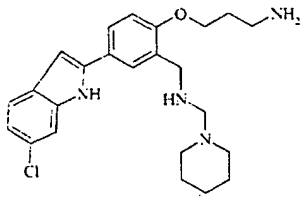
As example 158 using 1-(2-Aminoethyl)piperazine.
LC retention time 2.97 minutes, $[M+H]^+$ 442.

Example 160



As example 158 using 1-(2-Aminoethyl)piperidine.
LC retention time 2.99 minutes. $[M+H]^+$ 441.

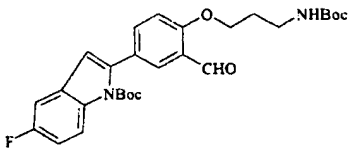
Example 161



As example 158 using 4-(Aminomethyl)piperidine.

LC retention time 3.00 minutes, $[M+H]^+$ 427.

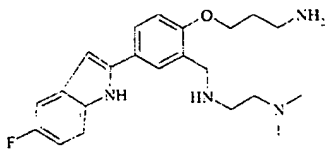
Example 162



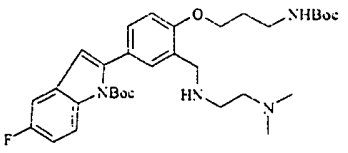
To a mixture of the aldehyde (1 eq) of example 10, dichlorobis(triphenylphosphine)-palladium(II) (10 mol%) and 2N Na_2CO_3 was added 5-fluoroindole-2-boronic acid (2 eq) in dry, degassed DME and the mixture heated at 80°C for 1h. After cooling to RT the solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid, which was purified by chromatography on silica gel eluting with mixtures of ethyl acetate and hexane.

LC retention time 5.31 minutes, $[M+H\text{-}Boc]^+$ 413.

Example 163



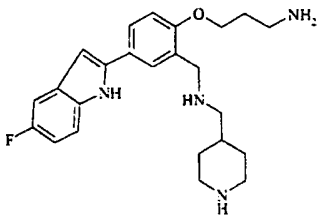
a)



The aldehyde (1 eq) from example 162 and N.N-Dimethylethylenediamine (1.6 eq) were stirred at RT for 15min in 1,2-dichloroethane, then sodium triacetoxyborohydride (1.5) was added in one portion. After stirring for 16h at RT the mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane and water. The organic layer was washed with brine and dried over $MgSO_4$. Concentration gave a solid. which was purified by chromatography on silica gel eluting with mixtures of dichloromethane and methanol.
LC retention time 3.59 minutes, $[M+H]^+$ 585.

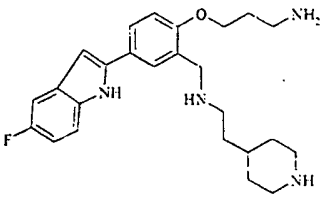
b) The bis-Boc compound was treated with 1mL of 1/1 DCM/TFA and stirred at RT for 10 min. The volatiles were removed *in vacuo* to give the desired compound as the tris-trifluoroacetate.
LC retention time 2.96 minutes, $[M+H]^+$ 385.

Example 164



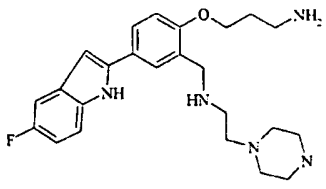
As example 163 using 4-(Aminomethyl)piperidine.
LC retention time 2.89 minutes. $[M+H]^+$ 411.

Example 165



As example 163 using 1-(2-Aminoethyl)piperidine.
LC retention time 2.93 minutes, $[M+H]^+$ 425.

Example 166



As example 163 using 1-(2-Aminoethyl)piperazine.
LC retention time 2.85 minutes, $[M+H]^+$ 426.

Tat-Tar Binding Inhibition Assay

Principle of the assay

To measure the inhibition by the compound of RNA binding to ADP-1, the RNA is titrated in the presence of a constant amount of fluorescent donor (fluorescein-ADP-1 peptide) and compound as described in International Patent Application WO99/64625. The assay is performed under competitive conditions. with a two fold excess of competitor RNA (a fully base-paired TAR sequence) over fluorescein-ADP-1 peptide (the fluorescent donor). The TAR RNA contains a 3' dabcyl group. The dabcyl group is a non-fluorescent acceptor for energy transfer from fluorescein (the fluorescent donor). When ADP-1 and RNA bind. the fluorescence signal from the fluorescein is quenched by the close proximity of the Dabcyl group. The presence of an inhibitory compound disrupts the ADP-1 RNA complex.

Complex disruption causes a decrease in energy transfer, which is observed as an increase in donor fluorescence intensity relative to a control (dabcyl) RNA-(fluorescein) ADP-1 binding reaction (in the absence of compound).

Disruption of DABCYL-TAR-FAM-ADP-1 complex formation by compounds of the invention.

Measurements were made in a 96-well plate reader (Wallac victor) with a fixed wavelength of 490nm and emission at 535 nm. I_0 was determined by an initial measurement of a 95 µL solution of 10nM Fluoresein-ADP-1 in the presence of 50mM Tris.HCl pH7.5, 80mM KCl ,1% DMSO 0.01% Triton X-100, 5µg/mL BSA , 20nM competitor RNA in the presence 1µM compound. I was then measured following the addition of 5 µL of a 20 X DABCYL-TAR RNA stock solution.

Example No.	Ki(µM)	Example No.	Ki(µM)	Example No.	Ki(µM)
2	<10	40	<10	87	<1
3	<10	42	<1	88	<10
4	<1	43	<1	89	<10
5	<10	44	<1	90	<50
6	<1	45	<50	91	<1
7	<10	46	<1	92	<10
8	<1	48	<10	93	<1
9	<1	49	<10	94	<1
11	<10	50	<10	95	<10
12	<10	51	<1	96	<1
13	<1	52	<50	98	<1
14	<1	54	<1	99	<10
15	<1	55	<50	100	<10
16	<10	56	<1	107	<1
17	<10	58	<10	108	<1
18	<1	59	<50	109	<10
19	<1	64	<1	110	<1

21	<1	65	<10	111	<1
22	<1	66	<1	112	<1
23	<1	68	<1	113	<1
24	<1	69	<10	116	<10
26	<1	70	<1	117	<10
27	<1	71	<10	118	<10
28	<50	74	<50	119	<50
29	<10	75	<50	120	<10
30	<10	77	<50	121	<10
31	<10	78	<50	126	<10
32	<10	79	<50	127	<10
33	<1	80	<10	129	<10
34	<10	81	<50	136	<10
35	<10	82	<100	137	<10
36	<1	83	<50	139	<1
37	<1	85	<1	140	<1
38	<10	72	<100		
39	<10	86	<10		

***In vitro* Translation assay**

Compounds of the present invention showed inhibitory activities in *in vitro* translation assays utilizing *E. coli* extracts. The plasmid pBestLuc, which contained the gene for firefly luciferase downstream of an *E. coli* promoter and a ribosome binding site was used as a template. The activity of the firefly luciferase enzyme resulted in a strong luminescent signal. The luminescence generated was a direct measurement of protein expression and of translation efficiency.

Translation reactions in the presence of compound were started by mixing a translation premix that contained Mg^{2+}, plasmid template, amino acids, nucleotidetriphosphates, phosphocreatine, creatine phosphokinase and folinic acid with the S30 extract that contains RNA polymerase, ribosomes and translation factors (prepared from *E.coli* MRE600 cells) followed by incubation at 37°C. The activity of the translated luciferase protein was

measured by adding an aliquot of the translation reaction to the non-luminescent substrate luciferin and the luminescence measured. The luminescence was quantified in a luminescence plate reader (Wallac Victor). Compounds were assayed 3-5 times over a range of concentrations and an IC_{50} calculated.

Example No.	8	13	14	15	51	85	98	110	112	113
IC_{50} (μM)	26.7	16.7	17.8	18.1	16.8	27.2	7.1	18.2	5.6	8.5

In vivo antibacterial assay

The *in vivo* therapeutic efficacy of the compounds of the invention is measured by intramuscular injection to mice experimentally infected with a pathogenic gram positive or gram negative bacterium (e.g. methicillin-resistant Staphylococcus aureus (MRSA), Clostridium difficile, Klebsiella pneumoniae, Eschericia coli, Haemophilus influenzae, etc.). As an example, MRSA strain A27223 can be used.

MRSA strain A27223 is prepared for experimental infection by growth on two large Brain Heart Infusion Agar plates. On each plate, 0.5 ml of frozen stock culture is plated out. Plates are then incubated for 18 hours at 30°C. The next day each plate is washed with 20 ml of Brain Heart Infusion Broth and then pooled together. A microscopic direct count of microorganisms is done using a 1:1000 dilution of plate wash. After a direct count is obtained, the number of organisms per milliliter is calculated. The count is adjusted to the desired amount of inoculum by diluting in 4% hog mucin. The desired challenge (amount of organisms given to mice) is 2.4×10^8 cfu/0.5 ml/mouse for MRSA strain A27223. The mice are infected intraperitoneally with 0.5 ml of challenge. Ten non-treated infected mice are used as controls. Mice used are adult male ICR mice. The average weight of the animals should range from 20 to about 26 grams.

Compounds are generally tested at 4 dose levels (e.g. 25, 6.25, 1.56 and 0.39 mg/kg) and prepared in 5% cremophor, unless otherwise specified. When MRSA A27223 is the challenging microorganism, vancomycin is used as the control compound, and is dosed at

6.25, 1.56, 0.39 and 0.098 mg/kg. It is prepared in 0.1M phosphate buffer. There are generally five infected mice per dose level, and they are treated with 0.2 ml of the test compound, preferably by intramuscular injection. Treatment begins 15 minutes and 2 hours post-infection.

A PD_{50} (protective dose-50, the dose of drug given which protects 50% mice from mortality) runs for 5 days. During this time, mortality of mice is checked every day and deaths are recorded. The cumulative mortality at each dose level is used to calculate a PD_{50} value for each compound. Surviving mice are sacrificed at the end of day 5 by CO_2 inhalation. The actual calculation of PD_{50} is performed with a computer program using the Spearman-Karber procedure.

A compound according to the invention is effective for the treatment of bacterial infection if it has a PD_{50} of about 100 mg/kg or less.

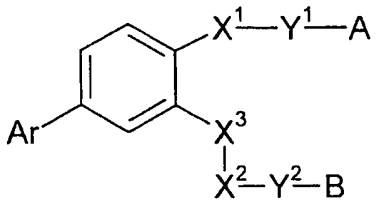
In vivo antiviral assay

The *in vivo* therapeutic efficacy of the compounds of the invention is measured by conventional *in vivo* antiviral assays including, but not limited to, that described in Letvin, N.L., Daniel, M.D., Sehgal, P.K., Desrosiers, R.C., Hunt, R.D., Waldron, L.M., MacKey, J.J., Schmidt, D.K., Chalifoux, L.V. and King, N.W. Introduction of AIDS-like disease in macaque monkeys with T-cell tropic retrovirus STLV-III, Science, 1985, 230, 71-73, which is incorporated herein by reference.

Variations, modifications, and other implementations of what is described herein will occur to those of ordinary skill in the art without departing from the spirit and scope of the invention as claimed. Accordingly, the invention is to be defined not by the preceding illustrative description but instead by the spirit and scope of the following claims.

CLAIMS:

1. A compound of the formula



wherein

Ar is an aryl group,

X^1 is selected from O, S, SO, SO_2, and NR,

X^2 is selected from O, S, SO, SO_2, NR and CR_2,

X^3 is CR_2,

Y^1 and Y^2 are independently selected from C_{1-12} alkylene, C_{4-12} arylene, C_{4-16} aralkylene, $CO(C_{1-12}$ alkylene), $CO(C_{4-12}$ arylene) and $CO(C_{4-16}$ aralkylene) groups,

A and B are independently selected from groups comprising a group selected from:

amine ($-NR_2$), amide ($-CONR_2$), amidine ($-C(=NR)NR_2$), thioamide ($-CSNR_2$), oxime (=NOR), hydroxylamine (-NHOR), hydroxamic acid (-CONROR), hydrazine ($-NRNR_2$), hydrazone ($=NNR_2$), sulphonamide ($-SO_2NR_2$), sulphinamide ($-SONR_2$), sulphoximine ($-SO(=NR)-$), urea ($-NRCONR_2$), guanidine ($-NRC(=NR)NR_2$), and aromatic and non-aromatic nitrogen heterocyclic groups,

each R is independently selected from H, C_{1-12} alkyl and C_{3-12} aryl, or any two R groups may together comprise a C_{1-6} alkylene chain,

or a pharmaceutically acceptable derivative thereof.

2. A compound according to claim 1 wherein X^1 is O.

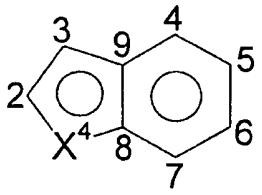
3. A compound according to claim 1 or 2 wherein X^2 is NR.

4. A compound according to claim 3 wherein X^2 is NH.

5. A compound according to any preceding claim wherein X^3 is CH_2.

6. A compound according to any preceding claim wherein Ar is a monocyclic or a fused bicyclic aromatic or heteroaromatic group.

7. A compound according to claim 6 wherein Ar is a fused bicyclic heteroaromatic group of the formula



wherein X^4 is NH, S or O.

8. A compound according to claim 7 wherein X^4 is NH.

9. A compound according to any preceding claim wherein Y^1 comprises a C_{1-5} alkylene group.

10. A compound according to any preceding claim wherein Y^2 comprises a C_{1-5} alkylene group.

11. A compound according to any preceding claim wherein A is a group comprising a group selected from amine, amidine, guanidine, and aromatic and non-aromatic nitrogen heterocyclic groups.

12. A compound according to any preceding claim wherein B is a group comprising a group selected from amine, amidine, guanidine, and aromatic and non-aromatic nitrogen heterocyclic groups.

13. A compound according to any one of claims 1 to 12 for use in therapy.

14. Use of a compound according to any one of claims 1 to 12 in the manufacture of a medicament for use in the treatment of viral infection or bacterial infection.

15. A method of treating viral infection or bacterial infection comprising administering to a patient in need of such treatment an effective dose of a compound according to any one of claims 1 to 12.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 in combination with a pharmaceutically acceptable excipient.

17. Use of a compound according to any one of claims 1 to 12 to inhibit the binding of Tat to Tar or to inhibit bacterial protein translation.

INTERNATIONAL SEARCH REPORT

Inter· ·onal Application No
PCT/GB 01/00362

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/26 C07D243/08 C07D333/16 C07D333/56 C07D307/80
C07D307/85 A61K31/155 A61K31/381 A61K31/343 A61K31/404
A61K31/4164 A61K31/445 A61K31/4025 A61K31/506 A61K31/501

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 580 402 A (SQUIBB & SONS INC) 26 January 1994 (1994-01-26) abstract ---	1,13-17
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CHANG, XINGRUO ET AL: "Studies on the chemical constituents of Glycyrrhiza. I. Isolation and structural elucidation of the antibacterial constituent, licobenzofuran" retrieved from STN Database accession no. 97:20701 XP002147477 abstract; figures & ZHONGCAOYAO (1981), 12(12), 530, --- -/--	1,13-15

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Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2001	11/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

1

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INTERNATIONAL SEARCH REPORT

Inter 'onal Application No
PCT/GB 01/00362

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5513 C07D209/12 C07D209/08 C07D213/30 C07D311/22
C07D215/14 C07D239/52 C07D209/42 C07D209/86 C07D277/24
C07C279/12 C07D295/20 C07D409/12 C07D401/12 C07D403/12

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B. FIELDS SEARCHED

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BARRON, D. I. ET AL: "Synthesis and antiinflammatory activity of 4-(p-biphenylyl)-3- hydroxybutyric acid and related compounds" J. MED. CHEM. (1968), 11(6), 1139-44, XP002147476 page 1140; examples 23-39; table I ---	1,13
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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/GB 01/00362

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P31/12 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 007, no. 034 (C-150), 10 February 1983 (1983-02-10) -& JP 57 188579 A (TAKEDA YAKUHIN KOGYO KK;OTHERS: 01), 19 November 1982 (1982-11-19) abstract page 622 -page 623; tables --- -/--	1,13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/GB 01/00362

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KUMAR S ET AL: "P-(CYCLOPENTENYL)PHENOL DERIVATIVES AS POTENTIAL BIODYNAMIC AGENTS" INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC, INCL. MEDICINAL,IN,PUBLICATIONS & INFORMATIONS DIRECTORATE, NEW DELHI, vol. 25B, 1968, pages 106-110, XP000909818 ISSN: 0019-5103 page 106, column 2, paragraph 3 page 107; examples 4-6 ---	1,13
A	WO 96 11902 A (ZENECA LTD ;BREAULT GLORIA ANN (GB); OLDFIELD JOHN (GB); TUCKER HO) 25 April 1996 (1996-04-25) claims 1,13 ---	1,13
A	GB 2 086 386 A (MAY & BAKER LTD) 12 May 1982 (1982-05-12) claims ---	1,13
A	WO 97 48674 A (ORTHO PHARMA CORP) 24 December 1997 (1997-12-24) abstract; claims ---	1,13-17
A	EP 0 574 808 A (THOMAE GMBH DR K) 22 December 1993 (1993-12-22) abstract; claims ---	1,13-17
A	EP 0 496 378 A (THOMAE GMBH DR K) 29 July 1992 (1992-07-29) abstract; claims ---	1,13-17
A	EP 0 144 892 A (HOECHST AG) 19 June 1985 (1985-06-19) claims ---	1,13-17
A	US 4 129 572 A (PIGEROL CHARLES ET AL) 12 December 1978 (1978-12-12) abstract; claim 1 column 5 -column 8; examples -----	1

1

Form PCT SA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ›nal Application No
PCT/GB 01/00362

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